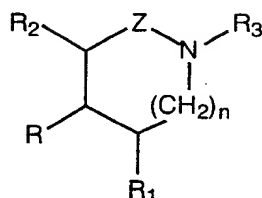


What is claimed is:

1. A compound of the formula:

5



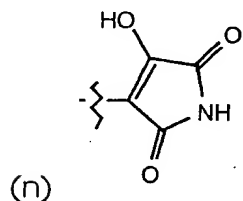
wherein

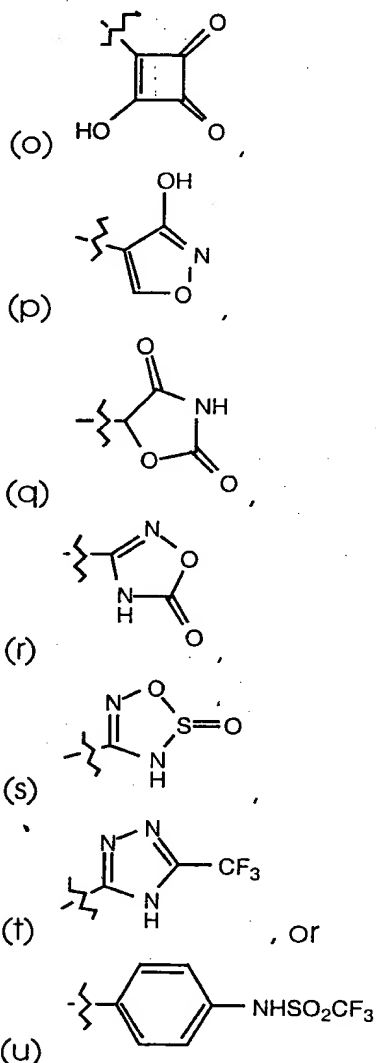
10 Z is -C(R<sub>18</sub>)(R<sub>19</sub>)- or -C(O)- wherein R<sub>18</sub> and R<sub>19</sub> are independently selected from hydrogen and loweralkyl;

n is 0 or 1;

R is -(CH<sub>2</sub>)<sub>m</sub>-W wherein m is an integer from 0 to 6 and W is

- 15 (a) -C(O)<sub>2</sub>-G wherein G is hydrogen or a carboxy protecting group,  
 (b) -PO<sub>3</sub>H<sub>2</sub>,  
 (c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,  
 (d) -CN,  
 (e) -C(O)NHR<sub>17</sub> wherein R<sub>17</sub> is loweralkyl,  
 (f) alkylaminocarbonyl,  
 20 (g) dialkylaminocarbonyl,  
 (h) tetrazolyl,  
 (i) hydroxy,  
 (j) alkoxy,  
 (k) sulfonamido,  
 25 (l) -C(O)NHS(O)<sub>2</sub>R<sub>16</sub> wherein R<sub>16</sub> is loweralkyl, haloalkyl, aryl or dialkylamino,  
 (m) -S(O)<sub>2</sub>NHC(O)R<sub>16</sub> wherein R<sub>16</sub> is defined as above,





- 5  $R_1$  and  $R_2$  are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, 10 alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and  $(R_{aa})(R_{bb})N-R_{cc}$  wherein  $R_{aa}$  is aryl or arylalkyl,  $R_{bb}$  is hydrogen or alkanoyl and  $R_{cc}$  is alkylene, with the proviso that one or both of  $R_1$  and  $R_2$  is other than hydrogen;
- 15  $R_3$  is (a)  $R_4-C(O)-R_5$ ,  $R_4-R_5a$ ,  $R_4-C(O)-R_5-N(R_6)$ ,  $R_6-S(O)_2-R_7$  or  $R_{26}-S(O)-R_{27}$  wherein  $R_5$  is (i) a covalent bond, (ii) alkylene, (iii) alkenylene, (iv)  $-N(R_{20})-R_8$  or  $-R_{8a}-N(R_{20})-R_8$
- 20

wherein  $R_8$  and  $R_{8a}$  are independently selected from the group consisting of alkylene and alkenylene and  $R_{20}$  is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl or cycloalkylalkyl or (v)  $-O-R_9-$  or  $-R_{9a}-O-R_9-$  wherein  $R_9$  and  $R_{9a}$  are independently selected from alkylene;

5  $R_{5a}$  is (i) alkylene or (ii) alkenylene;

$R_7$  is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv)  $-N(R_{21})-R_{10}-$  or  $-R_{10a}-N(R_{21})-R_{10}-$  wherein  $R_{10}$  and  $R_{10a}$  are independently selected from the group consisting of alkylene and alkenylene and  $R_{21}$  is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

10  $R_4$  and  $R_6$  are independently selected from the group consisting of

(i)  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from

- (1) hydrogen,
- (2) loweralkyl,
- (3) haloalkyl,
- 15 (4) alkoxyalkyl,
- (5) haloalkoxyalkyl,
- (6) alkenyl,
- (7) alkynyl,
- (8) cycloalkyl,
- 20 (9) cycloalkylalkyl,
- (10) aryl,
- (11) heterocyclic,
- (12) arylalkyl,
- (13) (heterocyclic)alkyl,
- 25 (14) hydroxyalkyl,
- (15) alkoxy,
- (16) aminoalkyl,
- (17) trialkylaminoalkyl,
- (18) alkylaminoalkyl,
- 30 (19) dialkylaminoalkyl, and
- (20) carboxyalkyl

(ii) loweralkyl,

(iii) alkenyl,

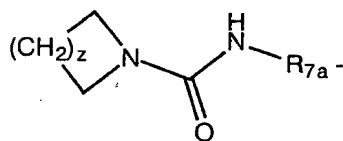
(iv) alkynyl,

35 (v) cycloalkyl,

(vi) cycloalkylalkyl,

(vii) aryl,

- (viii) arylalkyl,  
 (ix) heterocyclic,  
 (x) (heterocyclic)alkyl,  
 (xi) alkoxyalkyl,  
 5 (xii) hydroxyalkyl,  
 (xiii) haloalkyl,  
 (xiv) haloalkenyl,  
 (xv) haloalkoxyalkyl,  
 (xvi) haloalkoxy,  
 10 (xvii) alkoxyhaloalkyl,  
 (xviii) alkylaminoalkyl,  
 (xix) dialkylaminoalkyl,  
 (xx) alkoxy, and



- 15 (xxi)  
 wherein z is 0-5 and  $R_{7a}$  is alkylene;

$R_{26}$  is (i) loweralkyl, (ii) haloalkyl, (iii) alkenyl, (iv) alkynyl, (v) cycloalkyl, (vi) cycloalkylalkyl, (vii) aryl, (viii) arylalkyl, (ix) heterocyclic, (x) (heterocyclic)alkyl, (xi) alkoxyalkyl or (xii) alkoxy-substituted haloalkyl; and  
 20  $R_{27}$  is alkylene or alkenylene;

- (b)  $R_{22}-O-C(O)-R_{23}$ - wherein  $R_{22}$  is a carboxy protecting group or heterocyclic and  $R_{23}$  is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv)  $-N(R_{24})-R_{25}$ - wherein  $R_{25}$  is alkylene and  $R_{24}$  is hydrogen or loweralkyl,  
 25 (c) loweralkyl,  
 (d) alkenyl,  
 (e) alkynyl,  
 (f) cycloalkyl,  
 (g) cycloalkylalkyl,  
 30 (h) aryl,  
 (i) arylalkyl,  
 (j) aryloxyalkyl,  
 (k) heterocyclic,  
 (l) (heterocyclic)alkyl,  
 35 (m) alkoxyalkyl,

(n) alkoxyalkoxyalkyl, or

(o)  $R_{13}-C(O)-CH(R_{14})-$

wherein  $R_{13}$  is amino, alkylamino or dialkylamino and  $R_{14}$  is aryl or  $R_{15}-C(O)-$

wherein  $R_{15}$  is amino, alkylamino or dialkylamino;

5 or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 wherein n is 0 and Z is  $-CH_2-$ .

10 3. The compound according to Claim 1 wherein n is 1 and Z is  $-CH_2-$ .

4. The compound according to Claim 1 wherein n is 0, Z is  $-CH_2-$ ,  
and  $R_3$  is  $R_4-C(O)-R_5-$ ,  $R_6-SO_2-R_7-$  or  $R_{26}-S(O)-R_{27}-$  wherein  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_{26}$   
15 and  $R_{27}$  are as defined therein.

5. The compound according to Claim 1 wherein n is 0, Z is  $-CH_2-$ ,  
and  $R_3$  is alkoxyalkyl or alkoxyalkoxyalkyl.

20 6. The compound according to Claim 1 wherein n is 0, Z is  $-CH_2-$ ,  
and  $R_3$  is  $R_4-C(O)-R_5-$  wherein  $R_4$  is  $(R_{11})(R_{12})N-$  as defined therein and  $R_5$  is  
alkylene or  $R_3$  is  $R_6-S(O)_2-R_7-$  or  $R_{26}-S(O)-R_{27}-$  wherein  $R_7$  is alkylene,  $R_{27}$  is  
alkylene and  $R_6$  and  $R_{26}$  are as defined therein.

25 7. The compound according to Claim 1 wherein n is 0, Z is  $-CH_2-$   
and  $R_3$  is  $R_4-C(O)-N(R_{20})-R_8-$  or  $R_6-S(O)_2-N(R_{21})-R_{10}-$  wherein  $R_8$  and  $R_{10}$  are  
alkylene and  $R_4$ ,  $R_6$ ,  $R_{20}$  and  $R_{21}$  are as defined therein.

30 8. The compound according to Claim 1 wherein n is 0, R is tetrazolyl  
or  $-C(O)_2-G$  wherein G is hydrogen or a carboxy protecting group or R is  
tetrazolyl or R is  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl, haloalkyl or aryl, Z  
is  $-CH_2-$ ,  $R_1$  and  $R_2$  are independently selected from (i) loweralkyl, (ii)  
cycloalkyl, (iii) substituted and unsubstituted aryl wherein aryl is phenyl  
substituted with one, two or three substituents independently selected from  
35 loweralkyl, alkoxy, halo, alkoxyalkoxy and carboxyalkoxy, (iv) substituted or  
unsubstituted heterocyclic, (v) alkenyl, (vi) heterocyclic (alkyl), (vii)  
aryloxyalkyl, (viii) arylalkyl, (ix) (N-alkanoyl-N-alkyl)aminoalkyl, and (x)

alkylsulfonylamidoalkyl, and  $R_3$  is  $R_4-C(O)-R_5$ - wherein  $R_4$  is  $(R_{11})(R_{12})N$ - wherein  $R_{11}$  and  $R_{12}$  are independently selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, heterocyclic, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, aryl and arylalkyl and  $R_5$  is alkylene; or  $R_3$  is

- 5  $R_4-C(O)-N(R_{20})-R_8$ - or  $R_6-S(O)_2-N(R_{21})-R_{10}$ - wherein  $R_4$  is loweralkyl, aryl, alkoxy, alkylamino, aryloxy or arylalkoxy and  $R_6$  is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl,  $R_8$  and  $R_{10}$  are alkylene and  $R_{20}$  and  $R_{21}$  are loweralkyl; or  $R_3$  is  $R_6-S(O)_2-R_7$ - or  $R_{26}-S(O)-R_{27}$ - wherein  $R_6$  is loweralkyl or haloalkyl,  $R_7$  is alkylene,  $R_{26}$  is loweralkyl and  $R_{27}$  is alkylene.

10

9. The compound according to Claim 1 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl, haloalkyl or aryl,  $Z$  is  $-CH_2-$ ,  $R_1$  is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, 15 (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-*t*-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or 20 dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix) arylalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl,  $R_2$  is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, 25 dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl, or difluorophenyl, and  $R_3$  is  $R_4-C(O)-N(R_{20})-R_8$ - or  $R_6-S(O)_2-N(R_{21})-R_{10}$ - wherein  $R_8$  and  $R_{10}$  are alkylene,  $R_{20}$  and  $R_{21}$  are loweralkyl,  $R_4$  is loweralkyl, aryl, alkoxy, alkylamino, aryloxy or arylalkoxy and  $R_6$  is loweralkyl, haloalkyl, alkoxyalkyl, aryl or arylalkyl.

30

10. The compound according to Claim 1 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl, haloalkyl or aryl,  $Z$  is  $-CH_2-$ ,  $R_1$  is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, 35 (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl,

3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix) arylalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl or (xiii) alkylsulfonylamidoalkyl,  $R_2$  is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl, or difluorophenyl, and  $R_3$  is  $R_4-C(O)-R_5$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl, arylalkyl, heterocyclic, hydroxyalkyl, alkoxy, aminoalkyl, and trialkylaminoalkyl.

11. The compound according to Claim 1 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl, haloalkyl or aryl,  $Z$  is  $-CH_2-$ ,  $R_1$  is (i) loweralkyl (ii) alkenyl, (iii) arylalkyl, (iv) aryloxyalkyl, (v) heterocyclic, (vi) heterocyclic (alkyl), (vii) aryl, (viii) (N-alkanoyl-N-alkyl)aminoalkyl, or (viii) alkylsulfonylamidoalkyl,  $R_2$  is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and  $R_3$  is  $R_4-C(O)-R_5$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  is loweralkyl, and  $R_{12}$  is aryl or arylalkyl.

12. The compound according to Claim 1 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl, haloalkyl or aryl,  $Z$  is  $-CH_2-$ ,  $R_1$  is (i) phenyl or (ii) substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy, and carboxyalkoxy,  $R_2$  is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and  $R_3$  is

$R_6-S(O)_2-N(R_{21})-R_{10}$ - wherein  $R_{10}$  is alkylene,  $R_6$  is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl and  $R_{21}$  is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl.

- 5           13. The compound according to Claim 1 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl, haloalkyl or aryl,  $Z$  is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl or 1,4-benzodioxanyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy and alkoxyalkoxy,  $R_2$  is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and  $R_3$  is alkoxycarbonyl or  $R_6-S(O)_2-N(R_{21})-R_{10}$ - wherein  $R_{10}$  is alkylene,  $R_6$  is loweralkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and  $R_{21}$  is loweralkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl.
- 10           14. The compound according to Claim 1 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl or haloalkyl,  $Z$  is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,  $R_2$  is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and  $R_3$  is  $R_4-C(O)-R_5$ - wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N$ - wherein  $R_{11}$  and  $R_{12}$  are independently selected from loweralkyl, aryl, arylalkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic.
- 15           15. The compound according to Claim 1 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$
- 20           16. The compound according to Claim 1 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl or haloalkyl,  $Z$  is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,  $R_2$  is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and  $R_3$  is  $R_4-C(O)-R_5$ - wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N$ - wherein  $R_{11}$  and  $R_{12}$  are independently selected from loweralkyl, aryl, arylalkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic.
- 25           17. The compound according to Claim 1 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl or haloalkyl,  $Z$  is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,  $R_2$  is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and  $R_3$  is  $R_4-C(O)-R_5$ - wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N$ - wherein  $R_{11}$  and  $R_{12}$  are independently selected from loweralkyl, aryl, arylalkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic.
- 30           18. The compound according to Claim 1 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl or haloalkyl,  $Z$  is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,  $R_2$  is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and  $R_3$  is  $R_4-C(O)-R_5$ - wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N$ - wherein  $R_{11}$  and  $R_{12}$  are independently selected from loweralkyl, aryl, arylalkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic.
- 35           19. The compound according to Claim 1 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl or haloalkyl,  $Z$  is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,  $R_2$  is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and  $R_3$  is  $R_4-C(O)-R_5$ - wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N$ - wherein  $R_{11}$  and  $R_{12}$  are independently selected from loweralkyl, aryl, arylalkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic.



wherein  $R_{16}$  is loweralkyl or haloalkyl, Z is  $-CH_2-$ ,  $R_1$  is loweralkyl, alkoxyalkyl, or alkenyl,  $R_2$  is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and  $R_3$  is  $R_4-C(O)-R_5-$

- 5 wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from loweralkyl, aryl hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, heterocyclic, and arylalkyl.

- 10 16. The compound according to Claim 1 wherein n is 0, R is  $-C(O)_2-G$  wherein G is hydrogen or a carboxy protecting group, Z is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,  $R_2$  is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and  $R_3$  is  $R_4-C(O)-R_5-$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from loweralkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, aryl, and heterocyclic.

17. The compound according to Claim 1 wherein n is 0, R is  $-C(O)_2-G$  wherein G is hydrogen or a carboxy protecting group, Z is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,  $R_2$  is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and  $R_3$  is  $R_4-C(O)-R_5-$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  is loweralkyl and  $R_{12}$  is aryl.

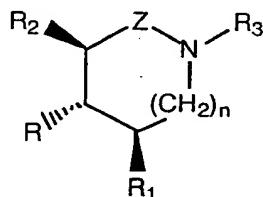
- 35 18. The compound according to Claim 1 wherein n is 0, R is  $-C(O)_2-G$  wherein G is hydrogen or a carboxy protecting group, Z is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-

- fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy,  $R_2$  is substituted or
- 5 unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and  $R_3$  is  $R_4-C(O)-R_5-$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  is alkyl
- 10 and  $R_{12}$  is selected from aryl, aminoalkyl, trialkylaminoalkyl, and heterocyclic.

19. A compound according to Claim 1 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group,  $Z$  is  $-CH_2-$ ,  $R_1$  is loweralkyl, alkenyl, heterocyclic (alkyl), aryloxyalkyl, aryalkyl, aryl, (N-alkanoyl-N-alkyl)aminoalkyl, or alkylsulfonylamidoalkyl, and  $R_3$  is  $R_4-C(O)-R_5-$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from alkyl, aryl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic.

20. A compound according to Claim 1 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group,  $Z$  is  $-CH_2-$ ,  $R_1$  is loweralkyl, alkenyl, heterocyclic (alkyl), aryloxyalkyl, aryalkyl, aryl, (N-alkanoyl-N-alkyl)aminoalkyl, or alkylsulfonylamidoalkyl, and  $R_3$  is  $R_4-C(O)-R_5-$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from alkyl, aryl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic, with the proviso that one or  $R_{11}$  and  $R_{12}$  is alkyl.

21. The compound according to Claim 1 of the formula:



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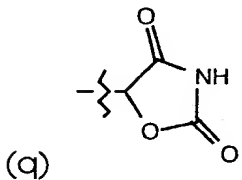
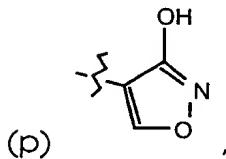
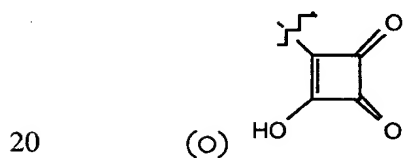
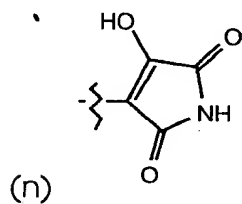
wherein

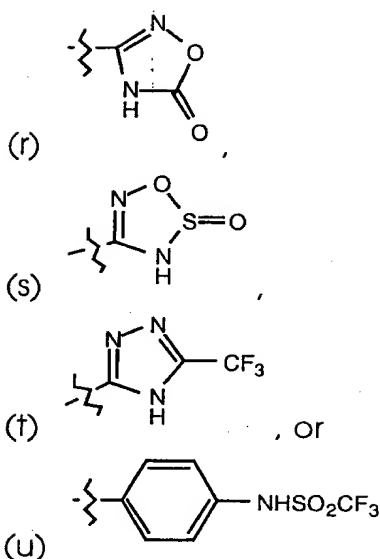
Z is  $-C(R_{18})(R_{19})-$  or  $-C(O)-$  wherein  $R_{18}$  and  $R_{19}$  are independently selected from hydrogen and loweralkyl;

n is 0 or 1;

R is  $-(CH_2)_m-W$  wherein m is an integer from 0 to 6 and W is

- 5 (a)  $-C(O)_2-G$  wherein G is hydrogen or a carboxy protecting group,
- (b)  $-PO_3H_2$ ,
- (c)  $-P(O)(OH)E$  wherein E is hydrogen, loweralkyl or arylalkyl,
- (d)  $-CN$ ,
- (e)  $-C(O)NHR_{17}$  wherein  $R_{17}$  is loweralkyl,
- 10 (f) alkylaminocarbonyl,
- (g) dialkylaminocarbonyl,
- (h) tetrazolyl,
- (i) hydroxy,
- (j) alkoxy,
- 15 (k) sulfonamido,
- (l)  $-C(O)NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl, haloalkyl, aryl or dialkylamino,
- (m)  $-S(O)_2NHC(O)R_{16}$  wherein  $R_{16}$  is defined as above,





- 5  $R_1$  and  $R_2$  are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl,
- 10 alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and  $(R_{aa})(R_{bb})N-R_{cc}-$  wherein  $R_{aa}$  is aryl or arylalkyl,  $R_{bb}$  is hydrogen or alkanoyl and  $R_{cc}$  is alkylene, with the proviso that one or both of  $R_1$  and  $R_2$  is other than
- 15 hydrogen;
- $R_3$  is (a)  $R_4-C(O)-R_5-$ ,  $R_4-R_{5a}-$ ,  $R_6-S(O)_2-R_7-$  or  $R_{26}-S(O)-R_{27}-$  wherein  $R_5$  is (i) a covalent bond, (ii) alkylene, (iii) alkenylene, (iv)  $-N(R_{20})-R_8-$  or  $-R_{8a}-N(R_{20})-R_8-$  wherein  $R_8$  and  $R_{8a}$  are independently selected from the group consisting of
- 20 alkylene and alkenylene and  $R_{20}$  is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl or cycloalkylalkyl or (v)  $-O-R_9-$  or  $-R_{9a}-O-R_9-$  wherein  $R_9$  and  $R_{9a}$  are independently selected from alkylene;
- $R_{5a}$  is (i) alkylene or (ii) alkenylene;
- 25  $R_7$  is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv)  $-N(R_{21})-R_{10}-$  or  $-R_{10a}-N(R_{21})-R_{10}-$

wherein  $R_{10}$  and  $R_{10a}$  are independently selected from the group consisting of alkylene and alkenylene and  $R_{21}$  is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

$R_4$  and  $R_6$  are independently selected from the group consisting of

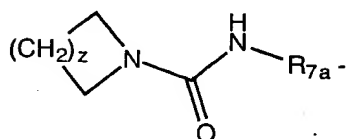
5 (i)  $(R_{11})(R_{12})N$ - wherein  $R_{11}$  and  $R_{12}$  are independently selected from

- (1) hydrogen,
- (2) loweralkyl,
- (3) haloalkyl,
- 10 (4) alkoxyalkyl,
- (5) haloalkoxyalkyl,
- (6) alkenyl,
- (7) alkynyl,
- (8) cycloalkyl,
- 15 (9) cycloalkylalkyl,
- (10) aryl,
- (11) heterocyclic,
- (12) arylalkyl,
- (13) (heterocyclic)alkyl,
- 20 (14) hydroxyalkyl,
- (15) alkoxy,
- (16) aminoalkyl, and
- (17) trialkylaminoalkyl,

- (ii) loweralkyl,
- 25 (iii) alkenyl,
- (iv) alkynyl,
- (v) cycloalkyl,
- (vi) cycloalkylalkyl,
- (vii) aryl,
- 30 (viii) arylalkyl,
- (ix) heterocyclic,
- (x) (heterocyclic)alkyl,
- (xi) alkoxyalkyl,
- (xii) hydroxyalkyl,
- 35 (xiii) haloalkyl,
- (xiv) haloalkenyl,
- (xv) haloalkoxyalkyl,

- (xvi) haloalkoxy,
- (xvii) alkoxyhaloalkyl,
- (xviii) alkylaminoalkyl,
- (xix) dialkylaminoalkyl,
- (xx) alkoxy, and

5



wherein z is 0-5 and  $R_{7a}$  is alkylene;

- 10  $R_{26}$  is (i) loweralkyl, (ii) haloalkyl, (iii) alkenyl, (iv) alkynyl, (v) cycloalkyl, (vi) cycloalkylalkyl, (vii) aryl, (viii) arylalkyl, (ix) heterocyclic, (x) (heterocyclic)alkyl, (xi) alkoxyalkyl or (xii) alkoxy-substituted haloalkyl; and  $R_{27}$  is alkylene or alkenylene;

- 15 (b)  $R_{22}-O-C(O)-R_{23}-$  wherein  $R_{22}$  is a carboxy protecting group or heterocyclic and  $R_{23}$  is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv)  $-N(R_{24})-R_{25}-$  wherein  $R_{25}$  is alkylene and  $R_{24}$  is hydrogen or loweralkyl,

- (c) loweralkyl,
- (d) alkenyl,
- 20 (e) alkynyl,
- (f) cycloalkyl,
- (g) cycloalkylalkyl,
- (h) aryl,
- (i) arylalkyl,
- 25 (j) aryloxyalkyl,
- (k) heterocyclic,
- (l) (heterocyclic)alkyl,
- (m) alkoxyalkyl,
- (n) alkoxyalkoxyalkyl, or
- 30 (o)  $R_{13}-C(O)-CH(R_{14})-$

wherein  $R_{13}$  is amino, alkylamino or dialkylamino and  $R_{14}$  is aryl or  $R_{15}-C(O)-$  wherein  $R_{15}$  is amino, alkylamino or dialkylamino;

or a pharmaceutically acceptable salt thereof.

22. The compound according to Claim 21 wherein n is 0 and Z is -CH<sub>2</sub>-.

5 23. The compound according to Claim 21 wherein n is 1 and Z is -CH<sub>2</sub>-.

24. The compound according to Claim 21 wherein n is 0, Z is -CH<sub>2</sub>-, and R<sub>3</sub> is R<sub>4</sub>-C(O)-R<sub>5</sub>-, R<sub>6</sub>-SO<sub>2</sub>-R<sub>7</sub>- or R<sub>26</sub>-S(O)-R<sub>27</sub>- wherein R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>26</sub> and R<sub>27</sub> are as defined therein.

25. The compound according to Claim 21 wherein n is 0, Z is -CH<sub>2</sub>-, and R<sub>3</sub> is alkoxyalkyl or alkoxyalkoxyalkyl.

15 26. The compound according to Claim 21 wherein n is 0, Z is -CH<sub>2</sub>-, and R<sub>3</sub> is R<sub>4</sub>-C(O)-R<sub>5</sub>- wherein R<sub>4</sub> is (R<sub>11</sub>)(R<sub>12</sub>)N- as defined therein and R<sub>5</sub> is alkylene or R<sub>3</sub> is R<sub>6</sub>-S(O)<sub>2</sub>-R<sub>7</sub>- or R<sub>26</sub>-S(O)-R<sub>27</sub>- wherein R<sub>7</sub> is alkylene, R<sub>27</sub> is alkylene and R<sub>6</sub> and R<sub>26</sub> are as defined therein.

20 27. The compound according to Claim 21 wherein n is 0, Z is -CH<sub>2</sub>- and R<sub>3</sub> is R<sub>4</sub>-C(O)-N(R<sub>20</sub>)-R<sub>8</sub>- or R<sub>6</sub>-S(O)<sub>2</sub>-N(R<sub>21</sub>)-R<sub>10</sub>- wherein R<sub>8</sub> and R<sub>10</sub> are alkylene and R<sub>4</sub>, R<sub>6</sub>, R<sub>20</sub> and R<sub>21</sub> are as defined therein.

28. The compound according to Claim 21 wherein n is 0, R is  
25 tetrazolyl or -C(O)<sub>2</sub>-G wherein G is hydrogen or a carboxy protecting group or R is tetrazolyl or R is -C(O)-NHS(O)<sub>2</sub>R<sub>16</sub> wherein R<sub>16</sub> is loweralkyl, haloalkyl or aryl, Z is -CH<sub>2</sub>-, R<sub>1</sub> and R<sub>2</sub> are independently selected from (i) loweralkyl, (ii) cycloalkyl, (iii) substituted and unsubstituted aryl wherein aryl is phenyl substituted with one, two or three substituents independently selected from  
30 loweralkyl, alkoxy, halo, alkoxyalkoxy and carboxyalkoxy and (iv) substituted or unsubstituted heterocyclic, (v) alkenyl, (vi) heterocyclic (alkyl), (vii) aryloxyalkyl, (viii) aryalkyl, (ix) (N-alkanoyl-N-alkyl)aminoalkyl, and (x) alkylsulfonylamidoalkyl, and R<sub>3</sub> is R<sub>4</sub>-C(O)-R<sub>5</sub>- wherein R<sub>4</sub> is (R<sub>11</sub>)(R<sub>12</sub>)N- wherein R<sub>11</sub> and R<sub>12</sub> are independently selected  
35 from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, heterocyclic, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, aryl and arylalkyl and R<sub>5</sub> is alkylene; or

$R_3$  is  $R_4-C(O)-N(R_{20})-R_8-$  or  $R_6-S(O)_2-N(R_{21})-R_{10}-$   
wherein  $R_4$  is loweralkyl, aryl, alkoxy, alkylamino, aryloxy or arylalkoxy and  
 $R_6$  is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl,  
 $R_8$  and  $R_{10}$  are alkylene and  $R_{20}$  and  $R_{21}$  are loweralkyl; or

- 5  $R_3$  is  $R_6-S(O)_2-R_7-$  or  $R_{26}-S(O)-R_{27}-$   
wherein  $R_6$  is loweralkyl or haloalkyl,  
 $R_7$  is alkylene,  
 $R_{26}$  is loweralkyl and  
 $R_{27}$  is alkylene.

10

29. The compound according to Claim 21 wherein  $n$  is 0,  $R$  is  
 $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  
 $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl, haloalkyl or aryl,  $Z$  is  $-CH_2-$ ,  $R_1$  is (i)  
loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl,  
15 (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-  
fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl,  
4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl,  
3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-  
hydroxyphenyl, 4-*t*-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or  
20 dihydrobenzofuranyl wherein the substituent is selected from alkoxy,  
alkoxyalkoxy and carboxyalkoxy, (ix) arylalkyl, (x) aryloxyalkyl, (xi) heterocyclic  
(alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl,  $R_2$  is  
substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl,  
1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl,  
25 benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or  
difluorophenyl and  $R_3$  is  $R_4-C(O)-N(R_{20})-R_8-$  or  $R_6-S(O)_2-N(R_{21})-R_{10}-$   
wherein  $R_8$  and  $R_{10}$  are alkylene,  
 $R_{20}$  and  $R_{21}$  are loweralkyl,  
 $R_4$  is loweralkyl, aryl, alkoxy, alkylamino, aryloxy or arylalkoxy and  
30  $R_6$  is loweralkyl, haloalkyl, alkoxyalkyl, aryl or arylalkyl.

30. The compound according to Claim 21 wherein  $n$  is 0,  $R$  is  
 $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  
 $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl, haloalkyl or aryl,  $Z$  is  $-CH_2-$ ,  $R_1$  is (i)  
35 loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl,  
(vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-  
fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl,



4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy,

- 5 alkoxyalkoxy and carboxyalkoxy, (ix) aryalkyl, (x) aryoxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl,  $R_2$  is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or  
10 difluorophenyl and  $R_3$  is  $R_4-C(O)-R_5-$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl, heterocyclic, hydroxyalkyl, alkoxy, aminoalkyl, and trialkylaminoalkyl.

- 15 31. The compound according to Claim 21 wherein n is 0, R is  $-C(O)_2-G$  wherein G is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl, haloalkyl or aryl, Z is  $-CH_2-$ ,  $R_1$  is (i) loweralkyl or (ii) alkenyl, (iii) aryalkyl, (iv) aryoxyalkyl, (v) heterocyclic (alkyl), (vi) aryl, (vii) (N-alkanoyl-N-alkyl)aminoalkyl, or (viii) alkylsulfonylamidoalkyl,  $R_2$   
20 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and  $R_3$  is  $R_4-C(O)-R_5-$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$   
25 wherein  $R_{11}$  is loweralkyl and  $R_{12}$  is aryl or arylalkyl.

32. The compound according to Claim 21 wherein n is 0, R is  $-C(O)_2-G$  wherein G is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl, haloalkyl or aryl, Z is  $-CH_2-$ ,  $R_1$  is (i)  
30 phenyl or (ii) substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy,  $R_2$  is substituted or  
35 unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the

substituent is selected from loweralkyl, alkoxy and halogen and  $R_3$  is  $R_6-S(O)_2-N(R_{21})-R_{10}$  wherein  $R_{10}$  is alkylene,  $R_6$  is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl and  $R_{21}$  is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl.

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33 The compound according to Claim 21 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl, haloalkyl or aryl,  $Z$  is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl or 1,4-benzodioxanyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy and alkoxyalkoxy,  $R_2$  is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and  $R_3$  is alkoxy carbonyl or  $R_6-S(O)_2-N(R_{21})-R_{10}$  wherein  $R_{10}$  is alkylene,  $R_6$  is loweralkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and  $R_{21}$  is loweralkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl.

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34. The compound according to Claim 21 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl or haloalkyl,  $Z$  is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,  $R_2$  is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and  $R_3$  is  $R_4-C(O)-R_5$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from loweralkyl, aryl arylalkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic.

35

35. The compound according to Claim 21 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group, tetrazolyl or  $-C(O)-NHS(O)_2R_{16}$  wherein  $R_{16}$  is loweralkyl or haloalkyl,  $Z$  is  $-CH_2-$ ,  $R_1$  is

loweralkyl, alkoxyalkyl or alkenyl,  $R_2$  is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and  $R_3$  is  $R_4-C(O)-R_5$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from loweralkyl, aryl, arylalkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic.

36. The compound according to Claim 21 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group,  $Z$  is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,  $R_2$  is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and  $R_3$  is  $R_4-C(O)-R_5$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from loweralkyl.

37. The compound according to Claim 21 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group,  $Z$  is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy,  $R_2$  is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and  $R_3$  is  $R_4-C(O)-R_5$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  is loweralkyl and  $R_{12}$  is aryl.

38. The compound according to Claim 21 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group,  $Z$  is  $-CH_2-$ ,  $R_1$  is substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or

dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy,  $R_2$  is substituted or

unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-

- 5 methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and  $R_3$  is  $R_6-S(O)_2-N(R_{21})-R_{10}$  wherein  $R_{10}$  is alkylene,  $R_6$  is loweralkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and  $R_{21}$  is loweralkyl, haloalkyl or alkoxyalkyl.

- 10 39. The compound according to Claim 21 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group,  $Z$  is  $-CH_2-$ ,  $R_1$  is loweralkyl, alkenyl, heterocyclic (alkyl), aryloxyalkyl, aryalkyl, aryl, (N-alkanoyl-N-alkyl)aminoalkyl, or alkylsulfonylamidoalkyl, and  $R_3$  is  $R_4-C(O)-R_5$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  and  $R_{12}$  are  
15 independently selected from alkyl, aryl, hydroxyalkyl, alkoxy, aminoalkyl, and heterocyclic.

40. A compound according to Claim 21 wherein  $n$  is 0,  $R$  is  $-C(O)_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group,  $Z$  is  $-CH_2-$ ,  $R_1$  is  
20 loweralkyl, alkenyl, heterocyclic (alkyl), aryloxyalkyl, aryalkyl, aryl, (N-alkanoyl-N-alkyl)aminoalkyl, or alkylsulfonylamidoalkyl, and  $R_3$  is  $R_4-C(O)-R_5$  wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from alkyl, aryl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic, with the proviso that one or  $R_{11}$  and  $R_{12}$  is alkyl

- 25 41. A compound selected from the group consisting of  
*trans-trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(3-(N-propyl-N-*n*-pentanesulfonylamino)propyl)pyrrolidine-3-carboxylic acid;  
*trans, trans*-2-(4-Methoxymethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;  
30 *trans, trans*-2-(3,4-Dimethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;  
*trans, trans*-2-(3,4-Dimethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-*n*-hexanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;  
35 *trans, trans*-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;

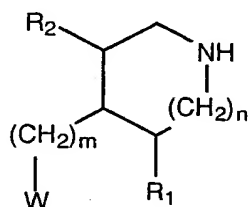
- trans,trans*-2-(3,4-Difluorophenyl)-4-(1,3-benzodioxol-5-yl)-1-(((N,N-di(*n*-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(3,4-Difluorophenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;
- 5 *trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-*n*-hexanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(3-chloropropanesulfonyl)amino)ethyl)-pyrrolidine-3-carboxylic acid;
- 10 *trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-isobutyl-N-(3-chloropropanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(4-methylbutanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid;
- 15 *trans,trans*-2-(4-Methoxy-3-fluorophenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(*n*-pentanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(2,2,3,3,3-pentafluoropropoxyethanesulfonyl)-amino)ethyl)pyrrolidine-3-carboxylic acid;
- 20 *trans,trans*-2-(1,4-Benzodioxan-6-yl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(*n*-pentanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid;
- 25 *trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-isobutyl-N-(pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-(2-methoxyethyl)-N-(3-chloropropanesulfonyl)amino)-ethyl)pyrrolidine-3-carboxylic acid;
- 30 *trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-(2-methoxyethyl)-N-(pentanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-((2,2,2-trifluoroethoxyethane)sulfonyl)amino)-ethyl)pyrrolidine-
- 35 3-carboxylic acid;

- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-(2-methoxyethyl)-N-(butanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid;
- 5 *trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(2-methylpropanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid; and
- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-isobutyl-N-(butanesulfonylamino))ethyl)pyrrolidine-3-carboxylic acid;
- 10 *trans,trans*-2-(2-Methylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2-(1,3-Dioxo-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 15 *trans,trans*-2-(2-(2-Tetrahydro-2H-pyran)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2,2,4-Trimethyl-3-pentenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2,2-Dimethyl-2-(1,3-dioxolan-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 20 *trans,trans*-2-(2-(1,3-Dioxo-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-((N-4-heptyl-N-(2-methyl-3-fluorophenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid
- 25 *trans,trans*-2-((2-Methoxyphenoxy)-methyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 30 *trans,trans*-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid
- 35 *trans,trans*-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

- trans,trans*-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2,2-dimethylpentyl)-4-(2,3-dihydro-benzofuran-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 5 *trans,trans*-2-(2,2,-Dimethyl-2-(1,3-dioxolan-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2-(2-Methoxyphenyl)-ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 10 *trans,trans*-2-(2,2-Dimethyl-3-(*E*)-pentenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2-(2-pyridyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- (*2S,3R,4S*)-2-(2-(2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 15 (*2S,3R,4S*)-2-(2-(2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2-(1-pyrazolyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 20 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;
- (*2R,3R,4S*)-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-pentanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid;
- 25 (*2S,3R,4S*)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- (*2S,3R,4S*)-2-(2,2-Dimethylpent-(*E*)-3-enyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 30 (*2S,3R,4S*)-2-(2,2-Dimethylpent-(*E*)-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- (*2S,3R,4S*)-2-((2-Methoxyphenoxy)-methyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid;
- (*2S,3R,4S*)-2-(2-(2-Methoxyphenyl)ethyl)-4(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid;
- 35 (554) *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-((bis-(o-tolyl)methyl)amino)carbonylmethyl)-( pyrrolidine-3-carboxylic acid;

- (555) *trans,trans*-2-[4-(2-methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-(2,2-dimethyl-1-phenylpropyl)-1-amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;  
 (556) *trans,trans*-2-[4-(2-methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-((bis-(o-tolyl)methyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;  
 5 (557) *trans,trans*-2-[4-(2-isopropoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-(2,2-dimethyl-1-phenylpropyl)-1-amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;  
 (558) *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(3,3-dimethyl-1-phenylbutyl)-1-amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;  
 (559) *trans,trans*-2-[4-(2-isopropoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-  
 10 ((1-(o-tolyl)-1-(o-ethylphenyl)-methyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;  
 (560) *trans,trans*-2-(4-(2-(2-propoxy)ethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-N-phenyl-N-t-butylhydrazino carbonylmethyl)-pyrrolidine-3-carboxylic acid; and  
 (561) *trans,trans*-2-(4-(2-methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-phenyl-N-t-butylhydrazino carbonylmethyl)-pyrrolidine-3-carboxylic acid;  
 15 or a pharmaceutically acceptable salt thereof.

42. A compound of the formula:



20

wherein n is 0 or 1;

m is 0 to 6;

W is (a) -C(O)<sub>2</sub>-G where G is hydrogen or a carboxy protecting group, (b) -PO<sub>3</sub>H<sub>2</sub>,

25

(c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) -C(O)NHR<sub>17</sub> where R<sub>17</sub> is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

30

(h) tetrazolyl,

(i) hydroxy,

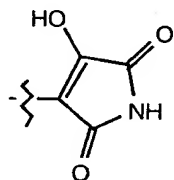
(j) alkoxy,

(k) sulfonamido,

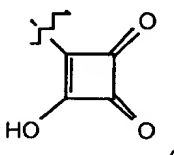


(l)  $-C(O)NHS(O)_2R_{16}$  where  $R_{16}$  is loweralkyl, haloalkyl, phenyl or dialkylamino,

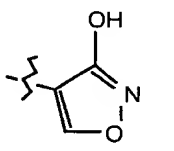
(m)  $-S(O)_2NHC(O)R_{16}$ .



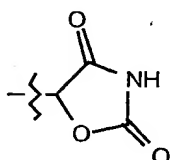
(n)



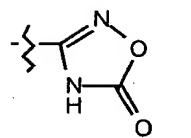
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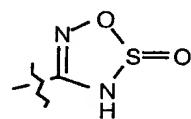
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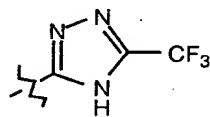
(q)



(r)

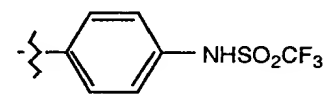


(s)



(t)

, or



(u)

; and

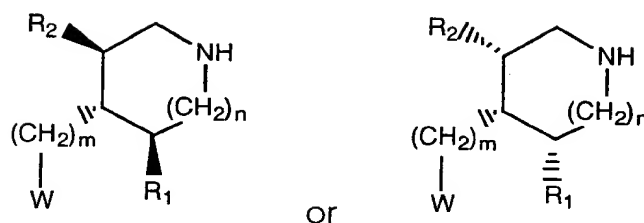
$R_1$  and  $R_2$  are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl,

alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and  $(R_{aa})(R_{bb})N-R_{cc}$  wherein  $R_{aa}$  is aryl or arylalkyl,  $R_{bb}$  is hydrogen or alkanoyl and  $R_{cc}$  is alkylene, with the proviso that one or both of  $R_1$  and  $R_2$  is other than hydrogen; or a salt thereof.

43. The compound of Claim 42 wherein  $m$  is zero or 1;  $W$  is  $-CO_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group; or the substantially pure (+)- or (-)-isomer thereof.

44. The compound of Claim 42 wherein  $n$  and  $m$  are both 0;  $W$  is  $-CO_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group; and  $R_1$  is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-*t*-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix) arylalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl, and  $R_2$  is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen; or the substantially pure (+)- or (-)-isomer thereof.

45. The compound according to Claim 42 of the formula:



wherein n is 0 or 1;

m is 0 to 6;

5 W is (a)  $-C(O)_2-G$  where G is hydrogen or a carboxy protecting group, (b)  $-PO_3H_2$ ,

(c)  $-P(O)(OH)E$  where E is hydrogen, loweralkyl or arylalkyl,

(d)  $-CN$ ,

(e)  $-C(O)NHR_{17}$  where  $R_{17}$  is loweralkyl,

10 (f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

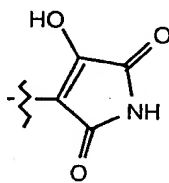
(i) hydroxy,

(j) alkoxy,

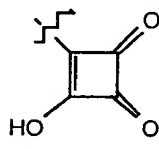
15 (k) sulfonamido,

(l)  $-C(O)NHS(O)_2R_{16}$  where  $R_{16}$  is loweralkyl, haloalkyl, phenyl or dialkylamino,

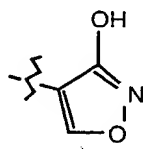
(m)  $-S(O)_2NHC(O)R_{16}$ .



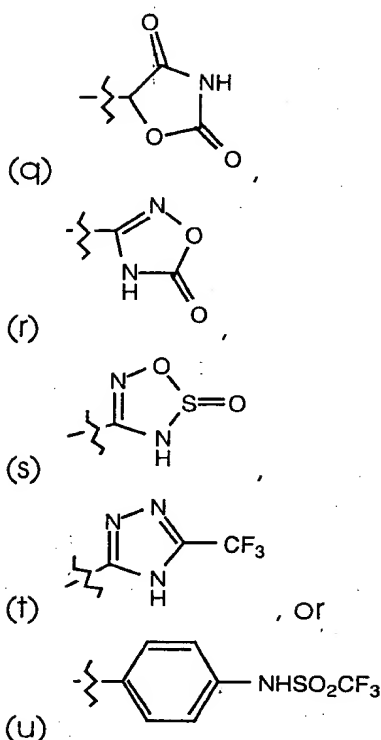
(n)



(o)



(p)



5 (u) ; and  
 R<sub>1</sub> and R<sub>2</sub> are independently selected from hydrogen, loweralkyl, alkenyl,  
 alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl,  
 haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl,  
 cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl,  
 10 dialkylaminocarbonylalkyl, aminocarbonylalkenyl,  
 alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl,  
 aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl,  
 alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and (R<sub>aa</sub>)(R<sub>bb</sub>)N-  
 R<sub>cc</sub>- wherein R<sub>aa</sub> is aryl or arylalkyl, R<sub>bb</sub> is hydrogen or alkanoyl and R<sub>cc</sub> is  
 15 alkylene, with the proviso that one or both of R<sub>1</sub> and R<sub>2</sub> is other than  
 hydrogen;  
 or a salt thereof.

46. The compound according to Claim 45 wherein  
 20 m is zero or 1;  
 W is -CO<sub>2</sub>-G wherein G is hydrogen or a carboxy protecting group; or  
 the substantially pure (+)- or (-)-isomer thereof.

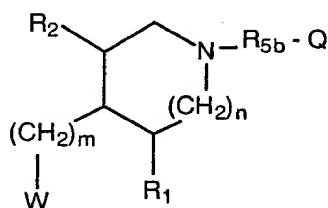
47. The compound according to Claim 45 wherein  
 25 n and m are both 0;

W is -CO<sub>2</sub>-G wherein G is hydrogen or a carboxy protecting group;  
and R<sub>1</sub> is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl,  
(vi) pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl,  
4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-  
5 methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-  
methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-  
methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl,  
1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected  
from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix)  
10 aryalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-  
alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl, and R<sub>2</sub> is substituted or  
unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-  
benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl,  
benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or  
15 difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and  
halogen; or  
the substantially pure (+)- or (-)-isomer thereof.

48. The substantially pure compound (+)-trans,trans-2-(4-  
20 Methoxyphenyl)-4-(1,3-benzodioxo-5-yl)pyrrolidine-3-carboxylic acid; or a salt  
or ester thereof.

49. The substantially pure compound (2S,3R,4S)-2-(2,2-  
Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-  
25 butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid; or a salt or ester  
thereof.

50. A compound of the formula



5 wherein n is 0 or 1;

m is 0 to 6;

R<sub>5b</sub> is alkylene;

Q is a leaving group;

W is (a) -C(O)<sub>2</sub>-G where G is hydrogen or a carboxy protecting group, (b)

10 -PO<sub>3</sub>H<sub>2</sub>,

(c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) -C(O)NHR<sub>17</sub> where R<sub>17</sub> is loweralkyl,

(f) alkylaminocarbonyl,

15 (g) dialkylaminocarbonyl,

(h) tetrazolyl,

(i) hydroxy,

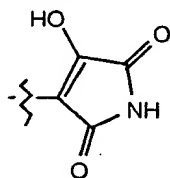
(j) alkoxy,

(k) sulfonamido,

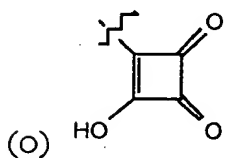
20 (l) -C(O)NHS(O)<sub>2</sub>R<sub>16</sub> where R<sub>16</sub> is loweralkyl, haloalkyl, phenyl or

dialkylamino,

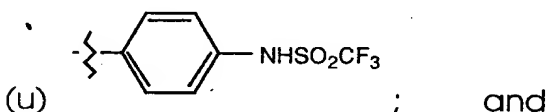
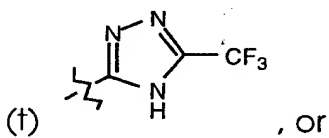
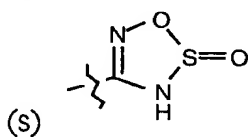
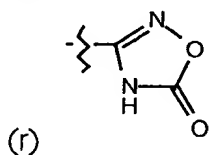
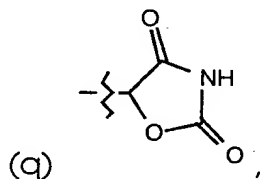
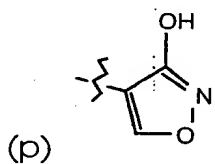
(m) -S(O)<sub>2</sub>NHC(O)R<sub>16</sub>.



(n)



(o)



$R_1$  and  $R_2$  are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and  $(R_{aa})(R_{bb})N-R_{cc}$  - wherein  $R_{aa}$  is aryl or arylalkyl,  $R_{bb}$  is hydrogen or alkanoyl and  $R_{cc}$  is alkylene, with the proviso that one or both of  $R_1$  and  $R_2$  is other than hydrogen; or a salt thereof.

51. The compound according to Claim 50 wherein

m is zero or 1;

R<sub>5b</sub> is alkylene;

Q is a leaving group; and

- 5 W is -CO<sub>2</sub>-G wherein G is hydrogen or a carboxy protecting group; or the substantially pure (+)- or (-)-isomer thereof.

52. The compound according to Claim 50 wherein

n and m are both 0;

- 10 R<sub>5b</sub> is alkylene;

Q is a leaving group;

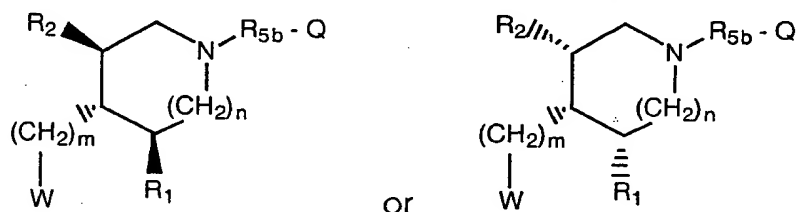
W is -CO<sub>2</sub>-G wherein G is hydrogen or a carboxy protecting group;

and R<sub>1</sub> is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl,

- 15 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy and R<sub>2</sub> is
- 20 substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and
- 25 halogen, (ix) aryalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl; or the substantially pure (+)- or (-)-isomer thereof.

53. The compound according to Claim 50 of the formula

30



wherein n is 0 or 1;



m is 0 to 6;

R<sub>5b</sub> is alkylene;

Q is a leaving group;

W is (a) -C(O)<sub>2</sub>-G where G is hydrogen or a carboxy protecting group, (b)

5 -PO<sub>3</sub>H<sub>2</sub>,

(c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) -C(O)NHR<sub>17</sub> where R<sub>17</sub> is loweralkyl,

(f) alkylaminocarbonyl,

10 (g) dialkylaminocarbonyl,

(h) tetrazolyl,

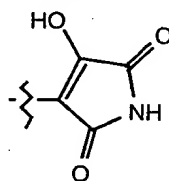
(i) hydroxy,

(j) alkoxy,

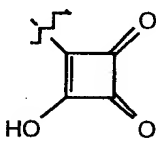
(k) sulfonamido,

15 (l) -C(O)NHS(O)<sub>2</sub>R<sub>16</sub> where R<sub>16</sub> is loweralkyl, haloalkyl, phenyl or dialkylamino,

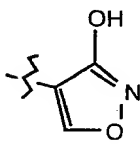
(m) -S(O)<sub>2</sub>NHC(O)R<sub>16</sub>,



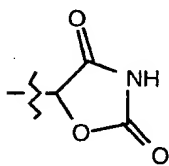
(n)



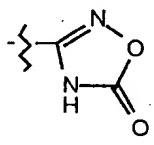
(o)



(p)

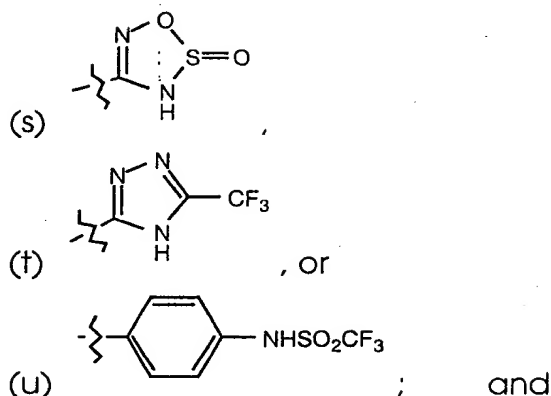


(q)



(r)

20



$R_1$  and  $R_2$  are independently selected from hydrogen, loweralkyl, alkenyl,

- 5 alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl,
- 10 aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and  $(R_{aa})(R_{bb})N-R_{cc}$  wherein  $R_{aa}$  is aryl or arylalkyl,  $R_{bb}$  is hydrogen or alkanoyl and  $R_{cc}$  is alkylene, with the proviso that one or both of  $R_1$  and  $R_2$  is other than hydrogen; or a salt thereof.

15

54. The compound according to Claim 53 wherein m is zero or 1;  $R_{5b}$  is alkylene; Q is a leaving group; W is  $-CO_2-G$  wherein G is hydrogen or a carboxy protecting group; or the substantially pure (+)- or (-)-isomer thereof.

20

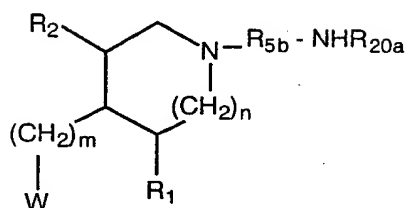
55. The compound according to Claim 53 wherein n and m are both 0;  $R_{5b}$  is alkylene; Q is a leaving group; W is  $-CO_2-G$  wherein G is hydrogen or a carboxy protecting group; and  $R_1$  is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl,

25 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy and  $R_2$  is

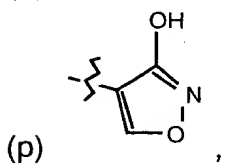
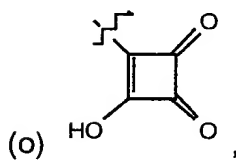
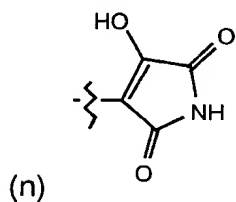
30 substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl,

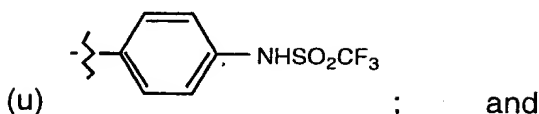
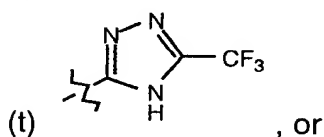
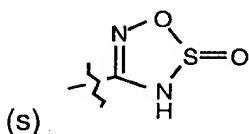
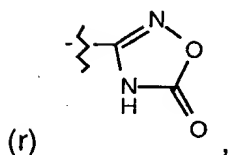
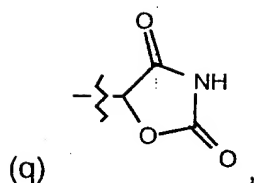
1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen, (ix) aryalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-  
5 N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl; or the substantially pure (+)- or (-)-isomer thereof.

56. A compound of the formula



- 5 wherein n is 0 or 1; m is 0 to 6; R<sub>5b</sub> is alkylene;  
R<sub>20a</sub> is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl,  
cycloalkyl, cycloalkylalkyl, aryl or arylalkyl;  
W is (a) -C(O)<sub>2</sub>-G where G is hydrogen or a carboxy protecting group, (b)  
-PO<sub>3</sub>H<sub>2</sub>,  
10 (c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,  
(d) -CN,  
(e) -C(O)NHR<sub>17</sub> where R<sub>17</sub> is loweralkyl,  
(f) alkylaminocarbonyl,  
(g) dialkylaminocarbonyl,  
15 (h) tetrazolyl,  
(i) hydroxy,  
(j) alkoxy,  
(k) sulfonamido,  
(l) -C(O)NHS(O)<sub>2</sub>R<sub>16</sub> where R<sub>16</sub> is loweralkyl, haloalkyl, phenyl or  
dialkylamino,  
20 (m) -S(O)<sub>2</sub>NHC(O)R<sub>16</sub>,



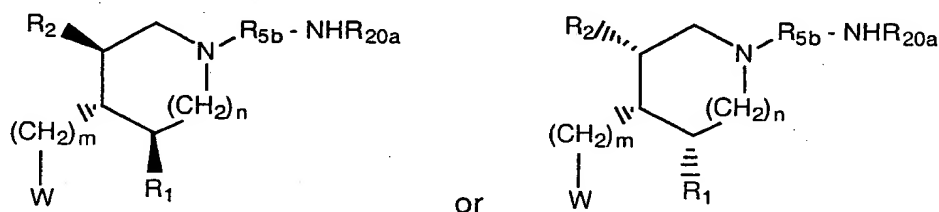


$R_1$  and  $R_2$  are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and  $(R_{aa})(R_{bb})N-R_{cc}$  wherein  $R_{aa}$  is aryl or arylalkyl,  $R_{bb}$  is hydrogen or alkanoyl and  $R_{cc}$  is alkylene, with the proviso that one or both of  $R_1$  and  $R_2$  is other than hydrogen; or a salt thereof.

57. The compound according to Claim 56 wherein  
 $m$  is zero or 1;  
 $R_{5b}$  is alkylene;  
 $R_{20a}$  is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl; and  
 $W$  is  $-CO_2-G$  wherein  $G$  is hydrogen or a carboxy protecting group; or the substantially pure (+)- or (-)-isomer thereof.

58. The compound according to Claim 56 wherein  
 n and m are both 0;  
 $R_{5b}$  is alkylene;  
 $R_{20a}$  is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl,  
 5 cycloalkyl, cycloalkylalkyl, aryl or arylalkyl;  
 W is  $-\text{CO}_2\text{-G}$  wherein G is hydrogen or a carboxy protecting group;  
 and  $R_1$  is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi)  
 pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-  
 10 fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-  
 trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-  
 4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-  
 butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein  
 the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and  
 carboxyalkoxy, (ix) arylalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-  
 15 N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl, and  $R_2$  is substituted or  
 unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-  
 methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl,  
 dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected  
 from loweralkyl, alkoxy and halogen; or  
 20 the substantially pure (+)- or (-)-isomer thereof.

59. The compound according to Claim 56 of the formula



- 25 wherein n is 0 or 1; m is 0 to 6;  $R_{5b}$  is alkylene;  $R_{20a}$  is hydrogen, loweralkyl, alkenyl,  
 haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl;  
 W is (a)  $-\text{C}(\text{O})_2\text{-G}$  where G is hydrogen or a carboxy protecting group, (b)  
 $-\text{PO}_3\text{H}_2$ ,  
 30 (c)  $-\text{P}(\text{O})(\text{OH})\text{E}$  where E is hydrogen, loweralkyl or arylalkyl,  
 (d)  $-\text{CN}$ ,  
 (e)  $-\text{C}(\text{O})\text{NHR}_{17}$  where  $R_{17}$  is loweralkyl,  
 (f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

(i) hydroxy,

(j) alkoxy,

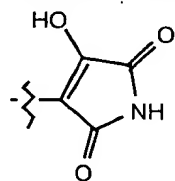
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(k) sulfonamido,

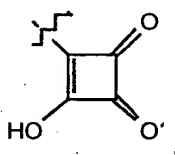
(l)  $-C(O)NHS(O)_2R_{16}$  where  $R_{16}$  is loweralkyl, haloalkyl, phenyl or

dialkylamino,

(m)  $-S(O)_2NHC(O)R_{16}$ .

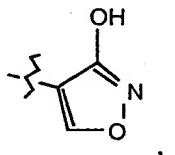


(n)

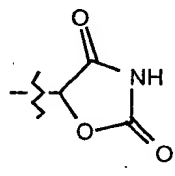


(o)

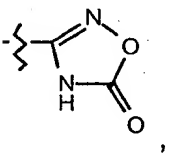
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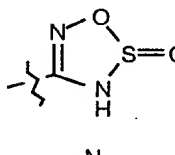
(p)



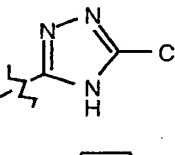
(q)



(r)

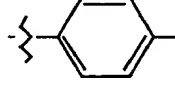


(s)



(t)

15



(u)

; and

$R_1$  and  $R_2$  are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and  $(R_{aa})(R_{bb})N-R_{cc}$  wherein  $R_{aa}$  is aryl or arylalkyl,  $R_{bb}$  is hydrogen or alkanoyl and  $R_{cc}$  is alkylene, with the proviso that one or both of  $R_1$  and  $R_2$  is other than hydrogen; or a salt thereof.

60. The compound according to Claim 59 wherein  
m is zero or 1;  
 $R_{5b}$  is alkylene;  
 $R_{20a}$  is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl; and  
W is  $-CO_2-G$  wherein G is hydrogen or a carboxy protecting group; or the substantially pure (+)- or (-)-isomer thereof.

61. The compound according to Claim 58 wherein  
n and m are both 0;  $R_{5b}$  is alkylene;  $R_{20a}$  is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl; W is  $-CO_2-G$  wherein G is hydrogen or a carboxy protecting group; and  $R_1$  is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix) arylalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl, and  $R_2$  is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen; or the substantially pure (+)- or (-)-isomer thereof.



62. A pharmaceutical composition for antagonizing the action of endothelin comprising a therapeutically effective amount of the compound of Claim 1 and a pharmaceutically acceptable carrier.

63. A pharmaceutical composition for antagonizing the action of endothelin comprising a therapeutically effective amount of the compound of Claim 21 and a pharmaceutically acceptable carrier.

64. A pharmaceutical composition for antagonizing the action of endothelin comprising a therapeutically effective amount of (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(*N,N*-di(*n*-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid and a pharmaceutically acceptable carrier.

65. A pharmaceutical composition for antagonizing the action of endothelin comprising a therapeutically effective amount of (2*S*,3*R*,4*S*)-2-3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(*N*-propyl-*N*-pentanesulfonyl)ethyl)-pyrrolidine-3-carboxylic acid and a pharmaceutically acceptable carrier.

66. A method for antagonizing the action of endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

67. A method for antagonizing the action of endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 21.

68. A method for antagonizing the action of endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(*N,N*-di(*n*-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid.

69. A method for antagonizing the action of endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*S*,3*R*,4*S*)-2-3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(*N*-propyl-*N*-pentanesulfonyl)ethyl)-pyrrolidine-3-carboxylic acid.

70. A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis, reperfusion injury, angina,  
5 pulmonary hypertension, migraine, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

71. A method for treating coronary angina, cerebral vasospasm, acute and  
10 chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders, ischemia-reperfusion injury, raynaud's disease and migraine comprising  
15 administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 1.

72. A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis, reperfusion injury, angina,  
20 pulmonary hypertension, migraine, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 21.

73. A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis, reperfusion injury, angina,  
25 pulmonary hypertension, migraine, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(*N,N*-di(*n*-butyl)aminocarbonylmethyl)-pyrrolidine-3-  
30 carboxylic acid.

74. A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis, reperfusion injury, angina,  
pulmonary hypertension, migraine, cerebral or myocardial ischemia or  
35 atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*S*,3*R*,4*S*)-2-3-Fluoro-4-methoxyphenyl)-4-(1,3-

benzodioxol-5-yl)-1-(2-(N-propyl-N-pentanesulfonyl)ethyl)-pyrrolidine-3-carboxylic acid.

5           75.    A method for treating coronary angina, cerebral vasospasm, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders,  
10 ischemia-reperfusion injury, raynaud's disease and migraine comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 21.

15           76.    A method for treating coronary angina, cerebral vasospasm, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders, ischemia-reperfusion injury, raynaud's disease and migraine comprising  
20 administering to a mammal in need of such treatment a therapeutically effective amount of a compound of (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(*N,N*-di(*n*-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid.

25           77.    A method for treating coronary angina, cerebral vasospasm, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders,  
30 ischemia-reperfusion injury, raynaud's disease and migraine comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of (2*S*,3*R*,4*S*)-2-3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-pentanesulfonyl)ethyl)-pyrrolidine-3-carboxylic acid.

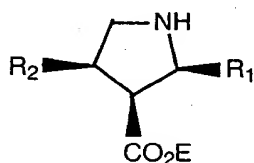
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78. A method for treating treating hypertension, congestive heart failure, restenosis following arterial injury, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1 in combination with one or more cardiovascular agents.

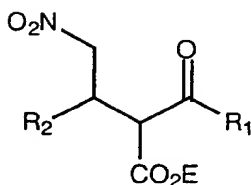
79. A method for treating treating hypertension, congestive heart failure, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 21 in combination with one or more cardiovascular agents.

80. A method for treating treating hypertension, congestive heart failure, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(*N*,*N*-di(*n*-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid in combination with one or more cardiovascular agents.

81. A process for the preparation of a compound of the formula:



wherein E is a carboxy-protecting group and R<sub>1</sub> and R<sub>2</sub> are independently selected from loweralkyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic and (heterocyclic)alkyl; or a salt thereof, comprising a) catalytic hydrogenation of a compound of the formula:



wherein E, R<sub>1</sub> and R<sub>2</sub> are defined as above and b) catalytic hydrogenation of the product of step a) in the presence of an acid or a mixture of acids.

5

82. The process of Claim 71 wherein E is loweralkyl, R<sub>1</sub> is aryl and R<sub>2</sub> is heterocyclic.

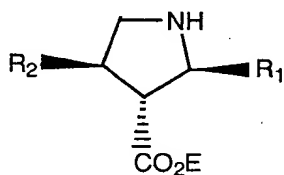
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83. The process of Claim 71 wherein the hydrogenation catalyst is Raney nickel and the acid is a mixture of acetic acid and trifluoroacetic acid.

84. The process of Claim 71 wherein E is loweralkyl, R<sub>1</sub> is 4-methoxyphenyl and R<sub>2</sub> is 1,3-benzodioxol-5-yl.

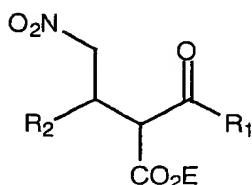
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85. A process for the preparation of a compound of the formula:



wherein E is a carboxy-protecting group and R<sub>1</sub> and R<sub>2</sub> are independently selected from loweralkyl, alkoxyalkyl, alkoxyalkylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic and (heterocyclic)alkyl; or a salt thereof, comprising

a) catalytic hydrogenation of a compound of the formula:



wherein E, R<sub>1</sub> and R<sub>2</sub> are defined as above,

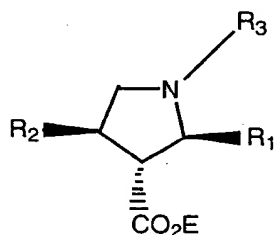
- b) catalytic hydrogenation of the product of step a) in the presence of an acid or a mixture of acids, and  
 5 c) epimerization of the product of step b) with a base.

86. The process of Claim 75 wherein E is loweralkyl, R<sub>1</sub> is aryl and R<sub>2</sub> is heterocyclic.  
 10

87. The process of Claim 75 wherein the hydrogenation catalyst is Raney nickel and the acid is a mixture of acetic acid and trifluoroacetic acid.

88. The process of Claim 75 wherein E is loweralkyl, R<sub>1</sub> is 4-methoxyphenyl and R<sub>2</sub> is 1,3-benzodioxol-5-yl.  
 15

89. A process for the preparation of a compound of the formula:



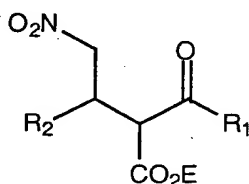
20 wherein E is a carboxy-protecting group, R<sub>1</sub> and R<sub>2</sub> are independently selected from loweralkyl, alkoxyalkyl, alkoxyalkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl,  
 25 aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic and (heterocyclic)alkyl and R<sub>3</sub> is R<sub>4</sub>-C(O)-R<sub>5</sub>-

wherein  $R_5$  is alkylene and  $R_4$  is  $(R_{11})(R_{12})N$ - wherein  $R_{11}$  and  $R_{12}$  are independently selected from

- (1) loweralkyl,
- (2) haloalkyl,
- 5 (3) alkoxyalkyl,
- (4) haloalkoxyalkyl,
- (5) alkenyl,
- (6) alkynyl,
- (7) cycloalkyl,
- 10 (8) cycloalkylalkyl,
- (9) aryl,
- (10) heterocyclic,
- (11) arylalkyl and
- (12) (heterocyclic)alkyl;
- 15 (13) hydroxyalkyl,
- (14) alkoxy,
- (15) aminoalkyl, and
- (16) trialkylaminoalkyl,

or a salt thereof, comprising

- 20 a) catalytic hydrogenation of a compound of the formula:



wherein E,  $R_1$  and  $R_2$  are defined as above,

- 25 b) catalytic hydrogenation of the product of step a) in the presence of an acid or a mixture of acids,
- c) epimerization of the product of step b) with a base and
- d) alkylation of the product of step c) with a compound of the formula  $R_3-X$  wherein X is a leaving group and  $R_3$  is defined as above.

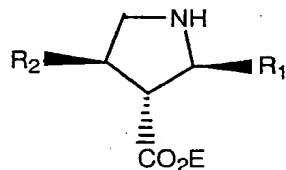
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90. The process of Claim 79 wherein E is loweralkyl,  $R_1$  is aryl,  $R_2$  is heterocyclic and  $R_3$  is  $-CH_2C(O)NR_{11}R_{12}$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from the group consisting of loweralkyl.

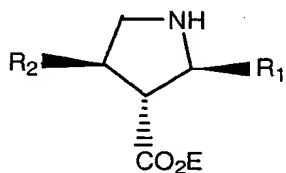
91. The process of Claim 79 wherein the hydrogenation catalyst is Raney nickel and the acid is a mixture of acetic acid and trifluoroacetic acid.

5 92. The process of Claim 79 wherein E is loweralkyl,  $R_1$  is 4-methoxyphenyl,  $R_2$  is 1,3-benzodioxol-5-yl,  $R_3$  is  $-\text{CH}_2\text{C}(\text{O})\text{N}(\text{n-Bu})_2$  and X is a halogen or sulfonate leaving group.

10 93. A process for the preparation of the substantially pure (+)-trans,trans optical isomer of the compound of the formula:



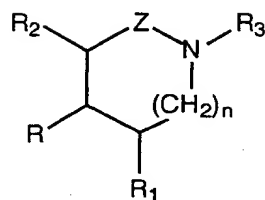
15 wherein E is loweralkyl,  $R_1$  is 4-methoxyphenyl and  $R_2$  is 1,3-benzodioxol-5-yl, or a salt thereof, comprising reacting a mixture of the (+) and (-) enantiomers of the compound of the formula:



20 wherein E is loweralkyl,  $R_1$  is 4-methoxyphenyl and  $R_2$  is 1,3-benzodioxol-5-yl with S-(+)- mandelic acid and separating the mandelate salt of the (+)-trans,trans optical isomer.

25 94. A compound of the formula:





wherein

Z is  $-C(R_{18})(R_{19})-$  or  $-C(O)-$  wherein R<sub>18</sub> and R<sub>19</sub> are independently selected from

5 hydrogen and loweralkyl;

n is 0 or 1;

R is  $-(CH_2)_m-W$  wherein m is an integer from 0 to 6 and W is

(a)  $-C(O)_2-G$  wherein G is hydrogen or a carboxy protecting group,

(b)  $-PO_3H_2$ ,

10 (c)  $-P(O)(OH)E$  wherein E is hydrogen, loweralkyl or arylalkyl,

(d)  $-CN$ ,

(e)  $-C(O)NHR_{17}$  wherein R<sub>17</sub> is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

15 (h) tetrazolyl,

(i) hydroxy,

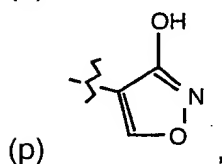
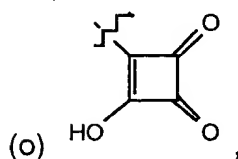
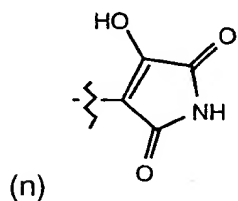
(j) alkoxy,

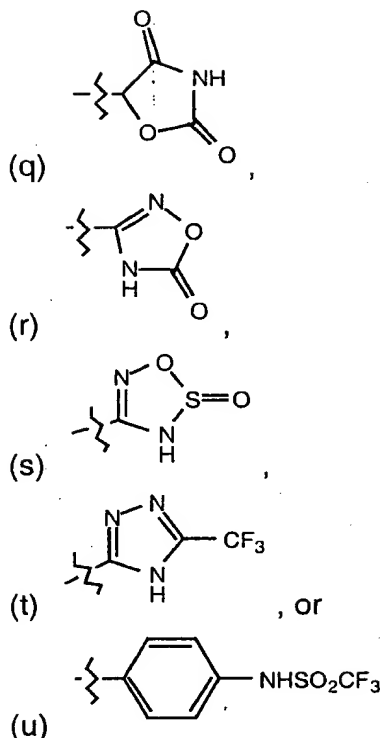
(k) sulfonamido,

(l)  $-C(O)NHS(O)_2R_{16}$  wherein R<sub>16</sub> is loweralkyl, haloalkyl, aryl or

20 dialkylamino,

(m)  $-S(O)_2NHC(O)R_{16}$  wherein R<sub>16</sub> is defined as above,





5  $R_1$  and  $R_2$  are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and  $(R_{aa})(R_{bb})N-R_{cc}$  - wherein  $R_{aa}$  is aryl or arylalkyl,  $R_{bb}$  is hydrogen or alkanoyl and  $R_{cc}$  is alkylene, with the proviso that one or both of  $R_1$  and  $R_2$  is other than hydrogen;

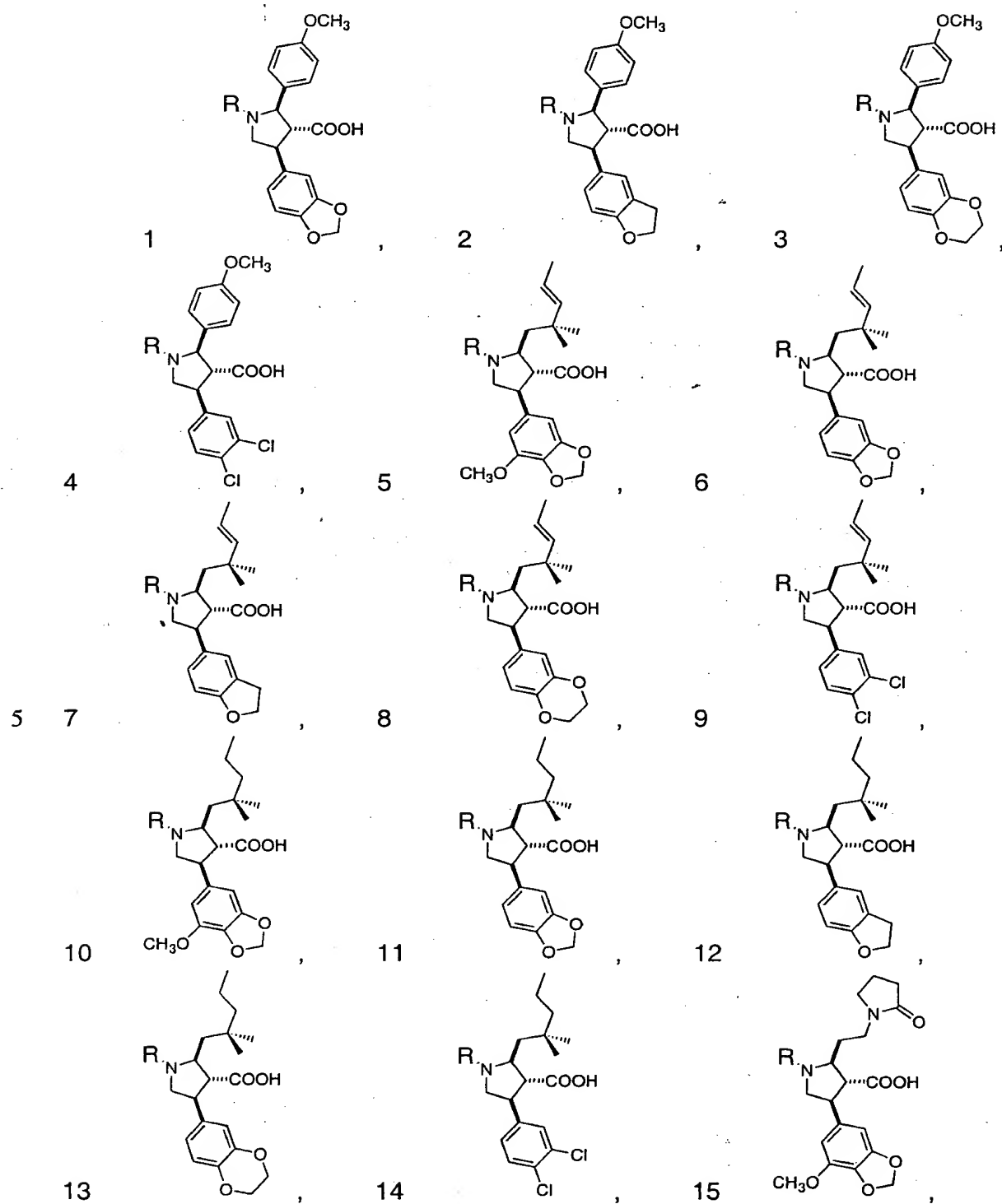
$R_3$  is (a)  $R_4-C(O)-R_5-$ ,  $R_4-C(O)-R_5-N(R_6)-$ , wherein  $R_5$  is (i) a covalent bond, (ii) alkylene, (iii) alkenylene, (iv)  $-N(R_{20})-R_8-$  or  $-R_{8a}-N(R_{20})-R_8-$  wherein  $R_8$  and  $R_{8a}$  are independently selected from the group consisting of alkylene and alkenylene and  $R_{20}$  is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl or cycloalkylalkyl or (v)  $-O-R_9-$  or  $-R_{9a}-O-R_9-$  wherein  $R_9$  and  $R_{9a}$  are independently selected from alkylene;

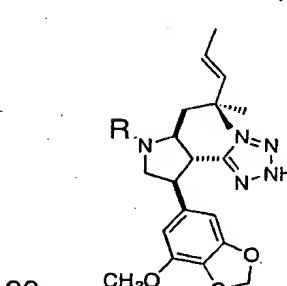
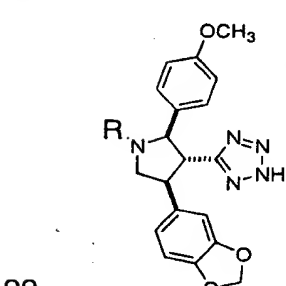
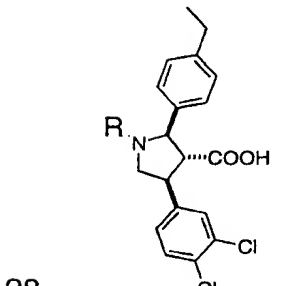
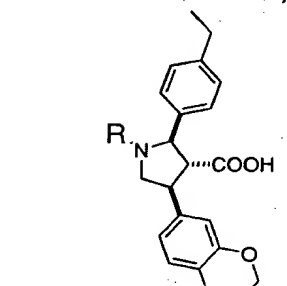
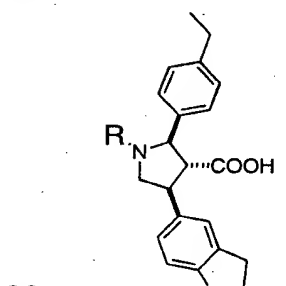
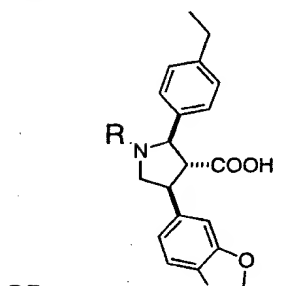
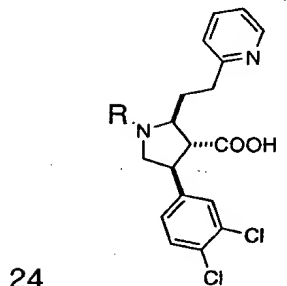
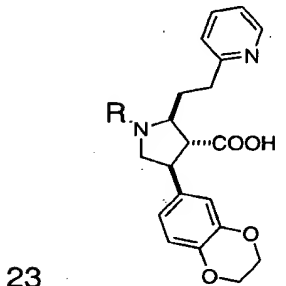
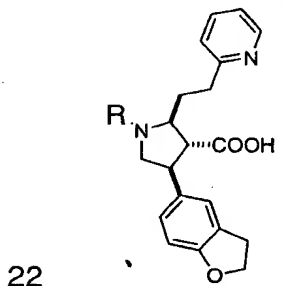
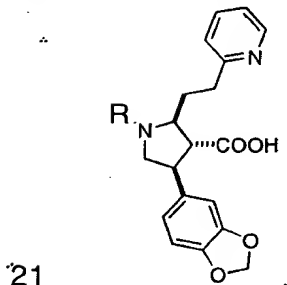
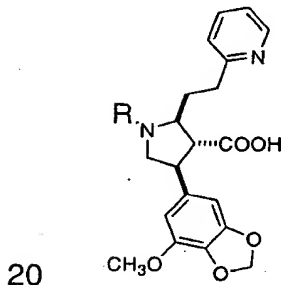
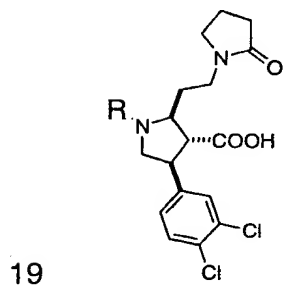
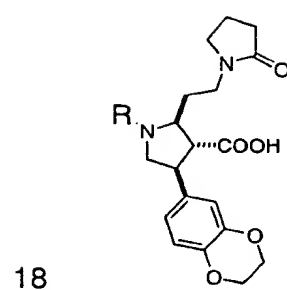
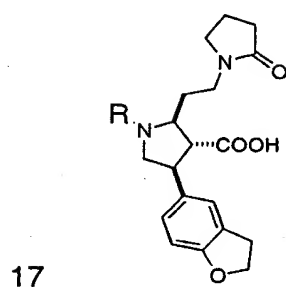
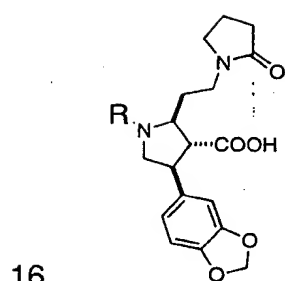
$R_4$  and  $R_6$  are  $(R_{11})(R_{12})N-$  wherein  $R_{11}$  and  $R_{12}$  are independently selected from

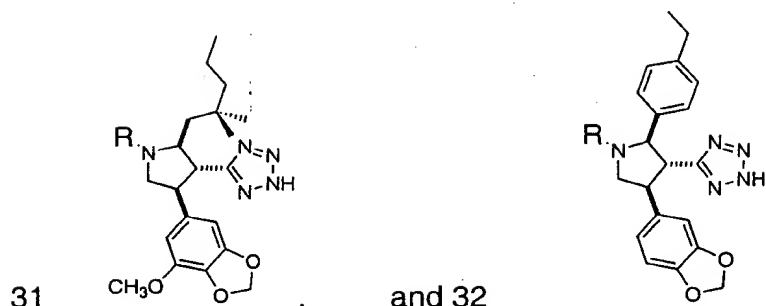
25 (1) hydrogen,

- 5 (2) loweralkyl,  
(3) haloalkyl,  
(4) alkoxyalkyl,  
(5) haloalkoxyalkyl,  
(6) alkenyl,  
(7) alkynyl,  
(8) cycloalkyl,  
(9) cycloalkylalkyl,  
10 (10) aryl,  
(11) heterocyclic,  
(12) arylalkyl,  
(13) (heterocyclic)alkyl,  
(14) hydroxyalkyl,  
(15) alkoxy,  
(16) aminoalkyl,  
(17) trialkylaminoalkyl,  
(18) alkylaminoalkyl,  
(19) dialkylaminoalkyl,  
20 (25) carboxyalkyl,  
(26) (cycloalkyl)aminoalkyl,  
(27) (cycloalkyl)alkylaminoalkyl,  
(28) (heterocyclic)aminoalkyl, and  
(29) (heterocyclic)aminoalkyl, with the proviso that at least one of  
25  $R_{11}$  and  $R_{12}$  is selected from heterocyclic, aminoalkyl,  
alkylaminoalkyl, dialkylaminoalkyl, trialkylaminoalkyl,  
alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl,  
(cycloalkyl)aminoalkyl, (cycloalkyl)alkylaminoalkyl,  
(heterocyclic)aminoalkyl, and (heterocyclic)alkylaminoalkyl;  
or a pharmaceutically acceptable salt thereof.  
30

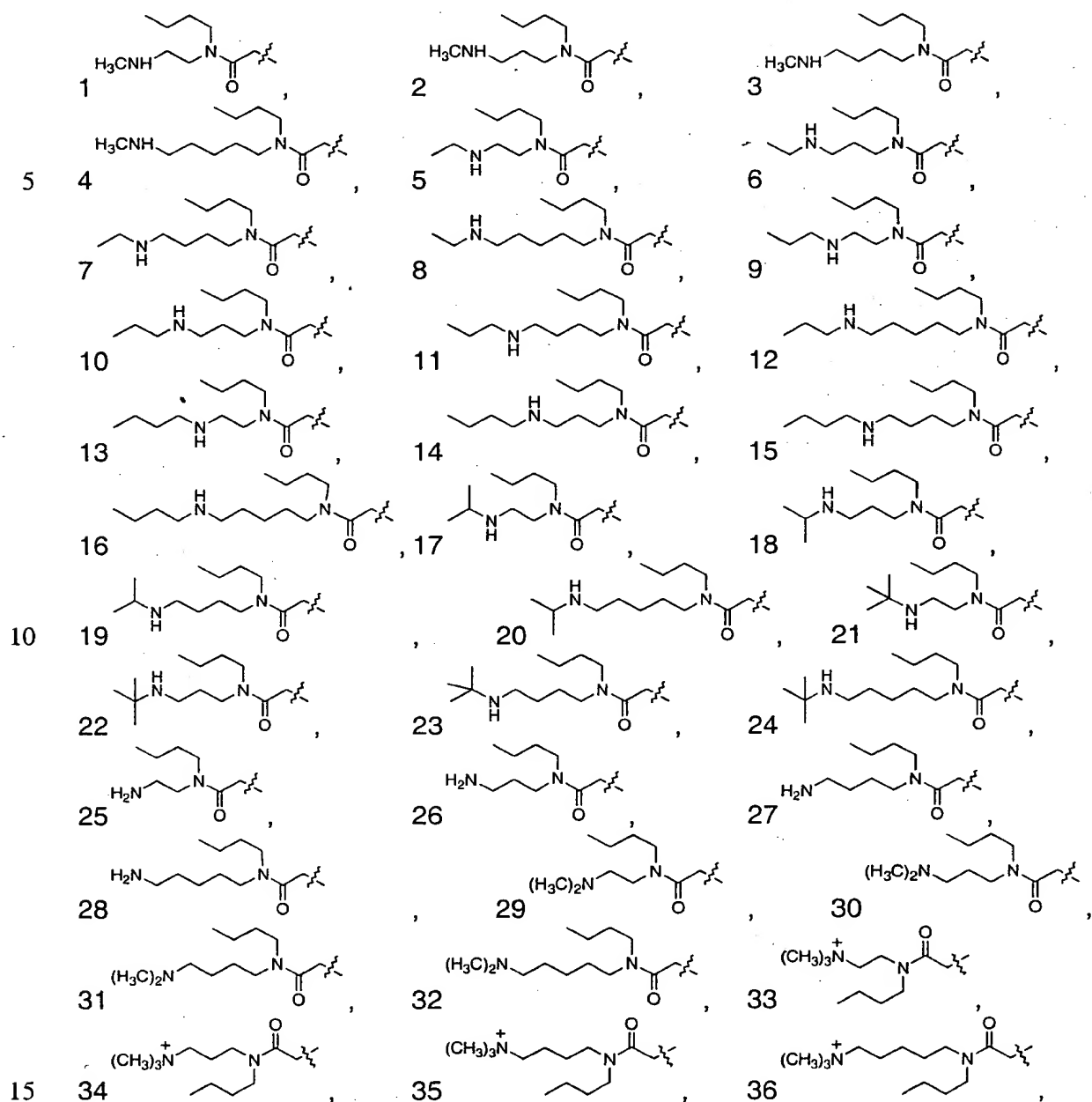
95. A compound selected from the group consisting of:

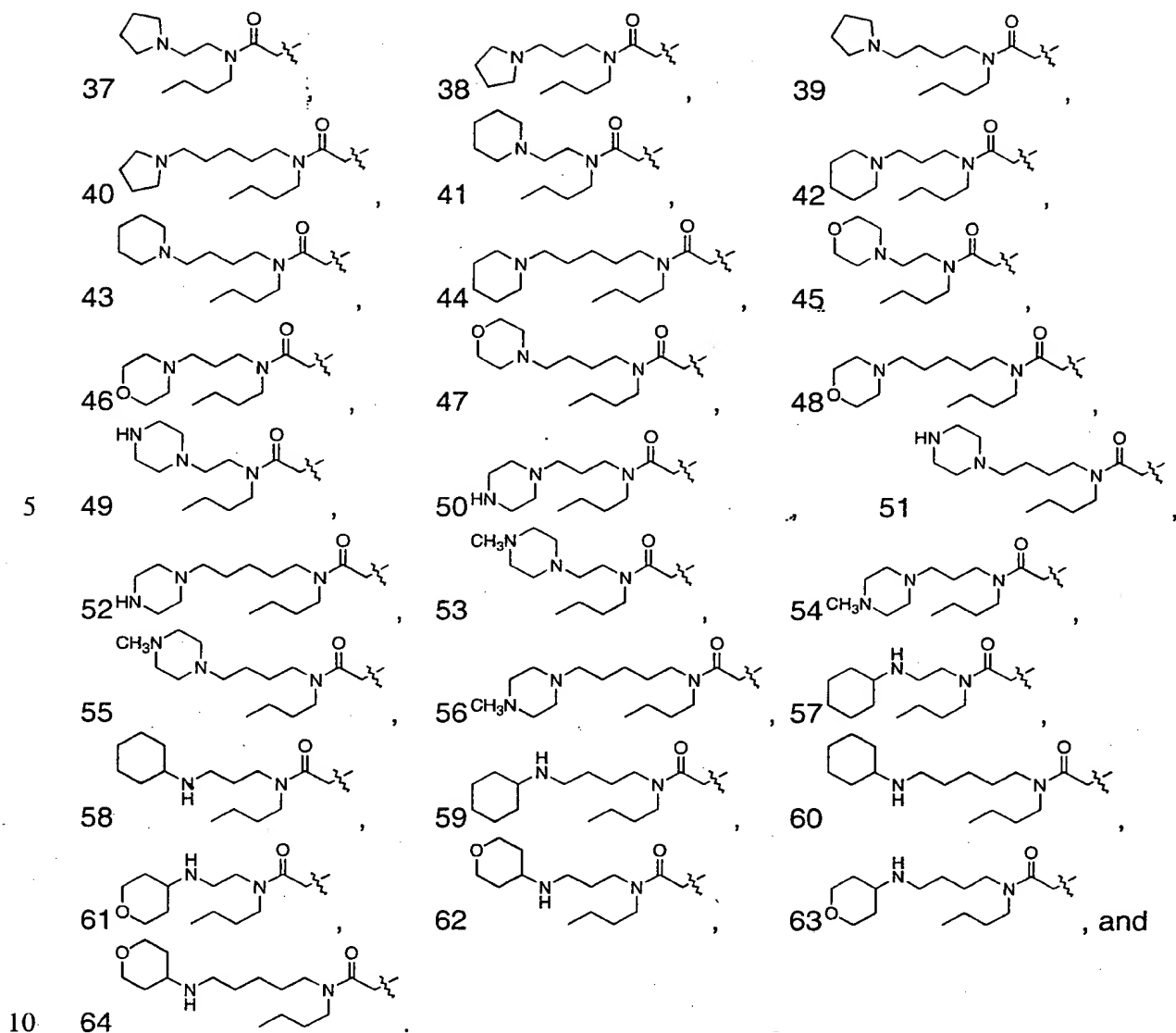






wherein R is selected from the group consisting of:





96. A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis, reperfusion injury, angina, pulmonary hypertension, migraine, cerebral or myocardial ischemia, atherosclerosis, coronary angina, cerebral vasospasm, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders, ischemia-reperfusion injury, Raynaud's disease, prostatic hyperplasia, and migraine comprising a therapeutically effective amount of a compound of claim 94, wherein said compound has an

attached charged functionality which reduces the degree of plasma protein binding of the compound.

5           97.    A method of improving the *in vivo* activity of compounds by reducing the amount of compound bound to protein by attaching a charged functionality to the compound.

          98.    A method of claim 97 wherein the charged functionality carries a positive charge at physiological pH.

10

          99.    A method for inhibiting bone metastases and metastatic growth in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

15

          100.   The method of Claim 99 wherein the bone metastases are osteoblastic.

          101.   The method of Claim 100 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

20

          102.   The method of Claim 101 wherein the primary cancer is prostate cancer and the patient is male.

25           103.   The method of Claim 99 which additionally comprises co-administration of an anticancer drug.

30           104.   The method of Claim 103 wherein the anticancer drug agent is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

          105.   The method of Claim 99 which additionally comprises the administration of radiation therapy.

35           106.   The method of Claim 99 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.



107. The method of Claim 106 wherein the therapeutic agent is a bisphosphonate.

108. The method of Claim 99 wherein the endothelin antagonist is an ET<sub>A</sub>-selective endothelin antagonist.

109. A method for the inhibition of bone loss in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

110. The method of Claim 109 wherein the patient has cancer.

111. The method of Claim 109 wherein the cancer is prostate cancer and the patient is male.

112. The method of Claim 109 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

113. The method of Claim 112 wherein the therapeutic agent is a bisphosphonate.

114. A method for the reduction of cancer-related pain in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

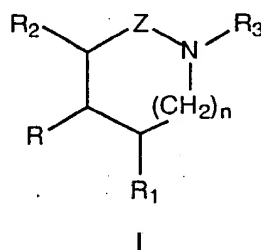
115. The method of Claim 114 wherein the cancer is prostate cancer and the patient is male.

116. The method of Claim 114 which additionally comprises the administration of an anticancer drug.

117. The method of Claim 116 wherein the anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

118. The method of Claim 115 which additionally comprises the administration of radiation therapy.

119. A method for inhibiting bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula I:



wherein

10 R is  $-(CH_2)_m-W$ ;

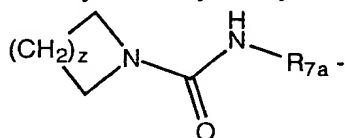
Z is selected from  $-C(R_{18})(R_{19})-$  and  $-C(O)-$ ;

R<sub>1</sub> and R<sub>2</sub> are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and  $(R_{aa})(R_{bb})N-R_{cc}$ ,

20 with the proviso that one or both of R<sub>1</sub> and R<sub>2</sub> is other than hydrogen;

R<sub>3</sub> is selected from R<sub>4</sub>-C(O)-R<sub>5</sub>-, R<sub>4</sub>-R<sub>5a</sub>-, R<sub>4</sub>-C(O)-R<sub>5</sub>-N(R<sub>6</sub>)-, R<sub>6</sub>-S(O)<sub>2</sub>-R<sub>7</sub>-, R<sub>26</sub>-S(O)-R<sub>27</sub>-, R<sub>22</sub>-O-C(O)-R<sub>23</sub>-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and R<sub>13</sub>-C(O)-CH(R<sub>14</sub>)-

25 R<sub>4</sub> and R<sub>6</sub> are independently selected from (R<sub>11</sub>)(R<sub>12</sub>)N-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



30 R<sub>5</sub> is selected from a covalent bond, alkylene, alkenylene,  $-N(R_{20})-R_8-$ ,  $-R_{8a}-N(R_{20})-R_8-$ ,  $-O-R_9-$ , and

-R<sub>9a</sub>-O-R<sub>9</sub>-;

R<sub>6</sub> is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R<sub>7</sub> is a covalent bond, alkylene, alkenylene -N(R<sub>21</sub>)-R<sub>10</sub>-, and -R<sub>10a</sub>-N(R<sub>21</sub>)-

5 R<sub>10</sub>-;

R<sub>8</sub> is selected from alkylene and alkenylene;

R<sub>9</sub> is alkylene;

R<sub>10</sub> is selected from alkylene and alkenylene;

10 R<sub>11</sub> and R<sub>12</sub> are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

R<sub>13</sub> is selected from amino, alkylamino and dialkylamino;

R<sub>14</sub> is selected from aryl and R<sub>15</sub>-C(O)-;

15 R<sub>15</sub> is selected from amino, alkylamino and dialkylamino;

R<sub>16</sub> is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

R<sub>17</sub> is loweralkyl;

R<sub>18</sub> and R<sub>19</sub> are independently selected from hydrogen and loweralkyl;

20 R<sub>20</sub> is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl and cycloalkylalkyl;

R<sub>21</sub> is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

R<sub>22</sub> is selected from a carboxy protecting group and heterocyclic;

R<sub>23</sub> is selected from covalent bond, alkylene, alkenylene and -N(R<sub>24</sub>)-R<sub>25</sub>-;

25 R<sub>24</sub> is selected from hydrogen and loweralkyl;

R<sub>25</sub> is alkylene;

R<sub>26</sub> is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy-substituted haloalkyl;

30 R<sub>27</sub> is selected from alkylene and alkenylene;

R<sub>5a</sub> is selected from alkylene and alkenylene;

R<sub>7a</sub> is alkylene;

R<sub>8a</sub> is selected from alkylene and alkenylene;

R<sub>9a</sub> is alkylene;

35 R<sub>10a</sub> is selected from alkylene and alkenylene;

R<sub>aa</sub> is selected from aryl and arylalkyl;

R<sub>bb</sub> is selected from hydrogen and alkanoyl;

$R_{CC}$  is alkylene;

m is 0-6;

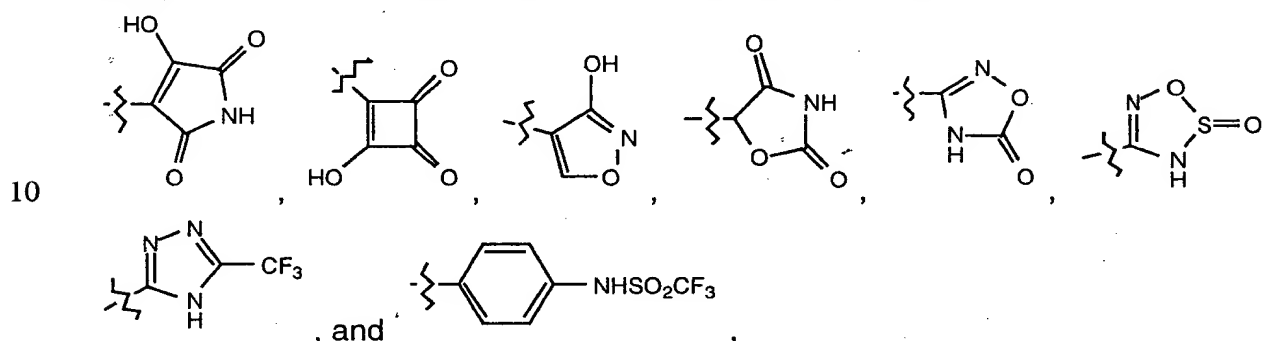
n is 0 or 1;

z is 0-5;

5 E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

W is selected from  $-C(O)_2-G$ ;  $-PO_3H_2$ ,  $-P(O)(OH)(E)$ ,  
 $-CN$ ,  $-C(O)NHR_{17}$ , alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy,  
 alkoxy, sulfonamido,  $-C(O)NHS(O)_2R_{16}$ ,  $-S(O)_2NHC(O)R_{16}$ ,



or a pharmaceutically acceptable salt thereof.

15 120. The method of Claim 119 wherein the bone metastases are osteoblastic.

121. The method of Claim 120 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

20 122. The method of Claim 121 wherein the primary cancer is prostate cancer and the patient is male.

25 123. The method of Claim 119 which additionally comprises the administration of an anticancer drug.

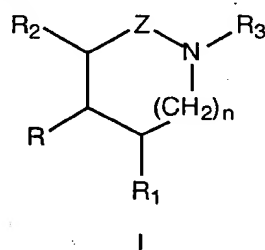
30 124. The method of Claim 123 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

125. The method of Claim 119 which additionally comprises the administration of radiation therapy.

126. The method of Claim 119 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

127. The method of Claim 126 wherein the therapeutic agent is a bisphosphonate.

128. A method for the inhibition of bone loss in cancer patients which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula I:



wherein,

R is  $-(CH_2)_m-W$ ;

Z is selected from  $-C(R_{18})(R_{19})-$  and  $-C(O)-$ ;

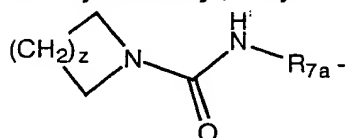
R<sub>1</sub> and R<sub>2</sub> are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and  $(R_{aa})(R_{bb})N-R_{cc}-$ ,

with the proviso that one or both of R<sub>1</sub> and R<sub>2</sub> is other than hydrogen;

R<sub>3</sub> is selected from R<sub>4</sub>-C(O)-R<sub>5</sub>-, R<sub>4</sub>-R<sub>5a</sub>-, R<sub>4</sub>-C(O)-R<sub>5</sub>-N(R<sub>6</sub>)-, R<sub>6</sub>-S(O)<sub>2</sub>-R<sub>7</sub>-, R<sub>26</sub>-S(O)-R<sub>27</sub>-, R<sub>22</sub>-O-C(O)-R<sub>23</sub>-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and R<sub>13</sub>-C(O)-CH(R<sub>14</sub>)-

R<sub>4</sub> and R<sub>6</sub> are independently selected from (R<sub>11</sub>)(R<sub>12</sub>)N-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl,

alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



R<sub>5</sub> is selected from a covalent bond, alkylene, alkenylene, -N(R<sub>20</sub>)-R<sub>8</sub>-, -R<sub>8a</sub>-  
 5 N(R<sub>20</sub>)-R<sub>8</sub>-, -O-R<sub>9</sub>-, and  
 -R<sub>9a</sub>-O-R<sub>9</sub>-;

R<sub>6</sub> is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R<sub>7</sub> is a covalent bond, alkylene, alkenylene -N(R<sub>21</sub>)-R<sub>10</sub>-, and -R<sub>10a</sub>-N(R<sub>21</sub>)-  
 10 R<sub>10</sub>-;

R<sub>8</sub> is selected from alkylene and alkenylene;

R<sub>9</sub> is alkylene;

R<sub>10</sub> is selected from alkylene and alkenylene;

R<sub>11</sub> and R<sub>12</sub> are independently selected from hydrogen, loweralkyl, haloalkyl,  
 15 alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl,  
 heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy,  
 aminoalkyl, trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

R<sub>13</sub> is selected from amino, alkylamino and dialkylamino;

R<sub>14</sub> is selected from aryl and R<sub>15</sub>-C(O)-;

R<sub>15</sub> is selected from amino, alkylamino and dialkylamino;

R<sub>16</sub> is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

R<sub>17</sub> is loweralkyl;

R<sub>18</sub> and R<sub>19</sub> are independently selected from hydrogen and loweralkyl;

R<sub>20</sub> is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl,  
 25 haloalkoxyalkyl, cycloalkyl and cycloalkylalkyl;

R<sub>21</sub> is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl,  
 haloalkoxyalkyl, aryl and arylalkyl;

R<sub>22</sub> is selected from a carboxy protecting group and heterocyclic;

R<sub>23</sub> is selected from covalent bond, alkylene, alkenylene and -N(R<sub>24</sub>)-R<sub>25</sub>-;

R<sub>24</sub> is selected from hydrogen and loweralkyl;

R<sub>25</sub> is alkylene;

R<sub>26</sub> is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl,  
 cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy-  
 substituted haloalkyl;

35 R<sub>27</sub> is selected from alkylene and alkenylene;

R<sub>5a</sub> is selected from alkylene and alkenylene;

R<sub>7a</sub> is alkylene;

R<sub>8a</sub> is selected from alkylene and alkenylene;

R<sub>9a</sub> is alkylene;

5 R<sub>10a</sub> is selected from alkylene and alkenylene;

R<sub>aa</sub> is selected from aryl and arylalkyl;

R<sub>bb</sub> is selected from hydrogen and alkanoyl;

R<sub>cc</sub> is alkylene;

m is 0-6;

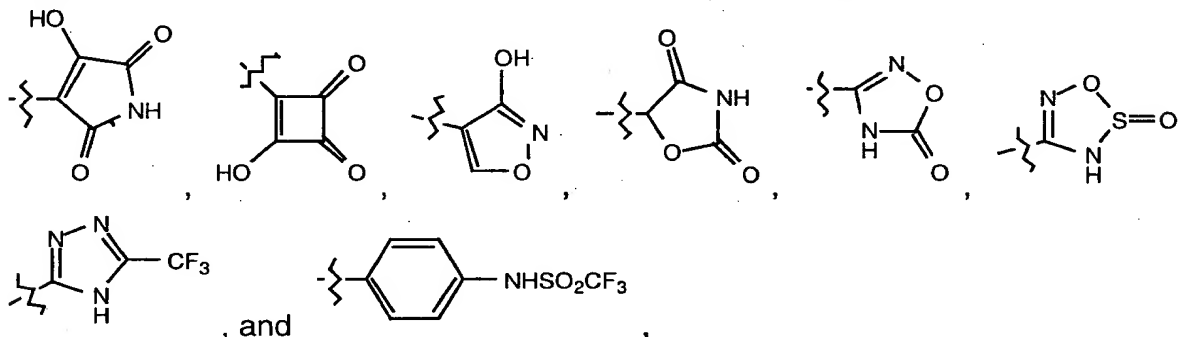
10 n is 0 or 1;

z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

15 W is selected from -C(O)<sub>2</sub>-G; -PO<sub>3</sub>H<sub>2</sub>; -P(O)(OH)(E),  
-CN, -C(O)NHR<sub>17</sub>, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy,  
alkoxy, sulfonamido, -C(O)NHS(O)<sub>2</sub>R<sub>16</sub>, -S(O)<sub>2</sub>NHC(O)R<sub>16</sub>,



or a pharmaceutically acceptable salt thereof.

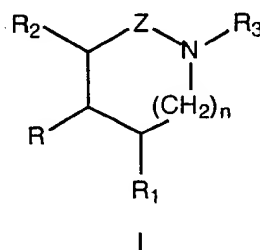
20

129. The method of Claim 128 wherein the cancer is prostate cancer and the patient is male.

25 130. The method of Claim 128 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

131. The method of Claim 130 wherein the therapeutic agent is a bisphosphonate.

132. A method for the reduction of cancer-related pain which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula I:



5

wherein

R is  $-(CH_2)_m-W$ ;

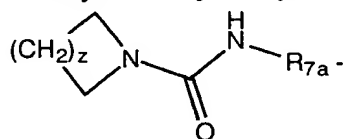
Z is selected from  $-C(R_{18})(R_{19})-$  and  $-C(O)-$ ;

10 R<sub>1</sub> and R<sub>2</sub> are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and (R<sub>aa</sub>)(R<sub>bb</sub>)N-R<sub>cc</sub>-;

15 with the proviso that one or both of R<sub>1</sub> and R<sub>2</sub> is other than hydrogen;

20 R<sub>3</sub> is selected from R<sub>4</sub>-C(O)-R<sub>5</sub>-, R<sub>4</sub>-R<sub>5a</sub>-, R<sub>4</sub>-C(O)-R<sub>5</sub>-N(R<sub>6</sub>)-, R<sub>6</sub>-S(O)<sub>2</sub>-R<sub>7</sub>- R<sub>26</sub>-S(O)-R<sub>27</sub>-, R<sub>22</sub>-O-C(O)-R<sub>23</sub>-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and R<sub>13</sub>-C(O)-CH(R<sub>14</sub>)-

25 R<sub>4</sub> and R<sub>6</sub> are independently selected from (R<sub>11</sub>)(R<sub>12</sub>)N-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



R<sub>5</sub> is selected from a covalent bond, alkylene, alkenylene,  $-N(R_{20})-R_8-$ ,  $-R_{8a}-N(R_{20})-R_8-$ ,  $-O-R_9-$ , and  $-R_{9a}-O-R_9-$ ;

30 R<sub>6</sub> is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;



R7 is a covalent bond, alkylene, alkenylene -N(R<sub>21</sub>)-R<sub>10</sub>-, and -R<sub>10a</sub>-N(R<sub>21</sub>)-R<sub>10</sub>-;

R8 is selected from alkylene and alkenylene;

R9 is alkylene;

5 R10 is selected from alkylene and alkenylene;

R11 and R12 are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

10 R13 is selected from amino, alkylamino and dialkylamino;

R14 is selected from aryl and R15-C(O)-;

R15 is selected from amino, alkylamino and dialkylamino;

R16 is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

R17 is loweralkyl;

15 R18 and R19 are independently selected from hydrogen and loweralkyl;

R20 is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl and cycloalkylalkyl;

R21 is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

20 R22 is selected from a carboxy protecting group and heterocyclic;

R23 is selected from covalent bond, alkylene, alkenylene and -N(R<sub>24</sub>)-R<sub>25</sub>-;

R24 is selected from hydrogen and loweralkyl;

R25 is alkylene;

25 R26 is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy-substituted haloalkyl;

R27 is selected from alkylene and alkenylene;

R<sub>5a</sub> is selected from alkylene and alkenylene;

R<sub>7a</sub> is alkylene;

30 R<sub>8a</sub> is selected from alkylene and alkenylene;

R<sub>9a</sub> is alkylene;

R<sub>10a</sub> is selected from alkylene and alkenylene;

R<sub>aa</sub> is selected from aryl and arylalkyl;

R<sub>bb</sub> is selected from hydrogen and alkanoyl;

35 R<sub>cc</sub> is alkylene;

m is 0-6;

n is 0 or 1;

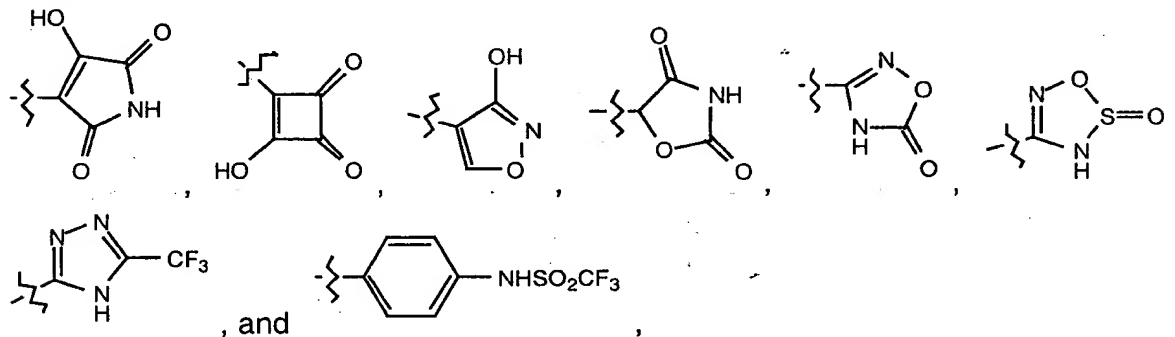
z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

W is selected from  $-C(O)_2G$ ,  $-PO_3H_2$ ,  $-P(O)(OH)(E)$ ,

- 5  $-CN$ ,  $-C(O)NHR_{17}$ , alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy, sulfonamido,  $-C(O)NHS(O)_2R_{16}$ ,  $-S(O)_2NHC(O)R_{16}$ ,



or a pharmaceutically acceptable salt thereof.

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133. The method of Claim 132 wherein the cancer is prostate cancer and the patient is male.

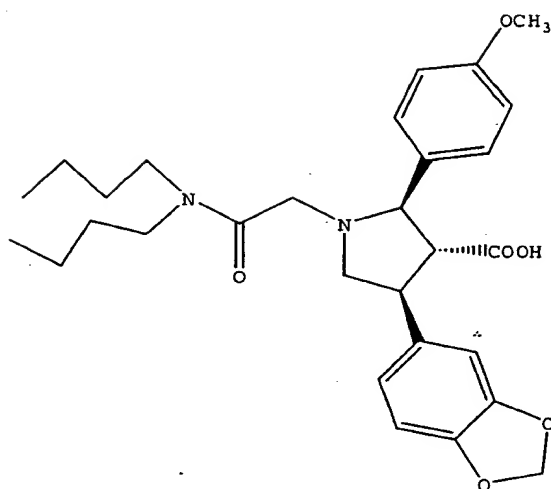
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134. The method of Claim 132 which additionally comprises the administration of an anticancer drug.

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135. The method of Claim 134 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

136. A method for inhibiting bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula IIIa



IIIa.

137. The method of Claim 136 wherein the bone metastases are osteoblastic.

138. The method of Claim 137 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

139. The method of Claim 138 wherein the primary cancer is prostate cancer and the patient is male.

140. The method of Claim 138 which additionally comprises the administration of an anticancer drug.

141. The method of Claim 140 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

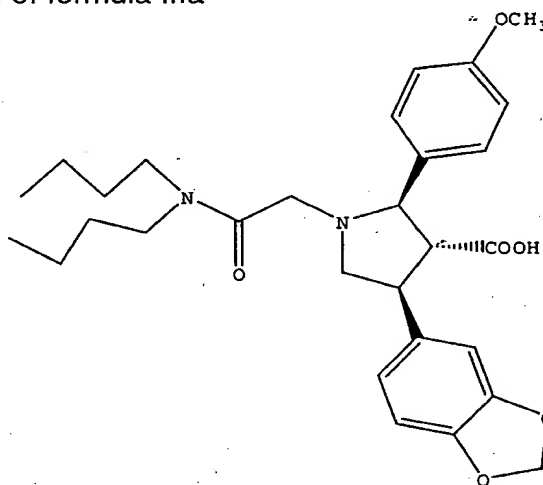
142. The method of Claim 138 which additionally comprises the administration of radiation therapy.

143. The method of Claim 138 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

144. The method of Claim 143 wherein the agent is a bisphosphonate.

145. The method of Claim 138 wherein the endothelin antagonist is an ET<sub>A</sub>-selective endothelin antagonist.

5 146. A method for the inhibition of bone loss in cancer patients which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula IIIa



IIIa.

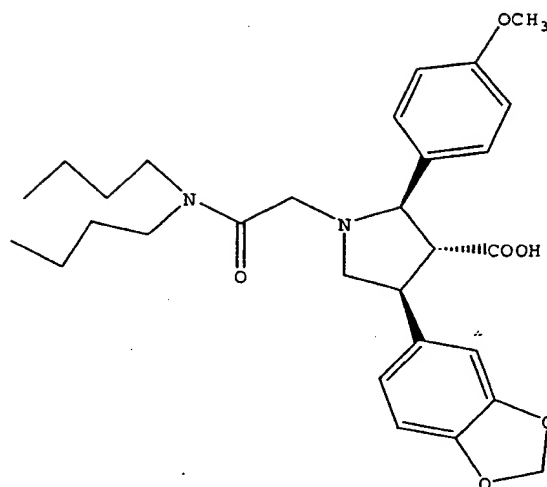
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147. The method of Claim 146 wherein the cancer is prostate cancer and the patient is male.

15 148. The method of Claim 146 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

149. The method of Claim 148 wherein therapeutic agent is a bisphosphonate.

20 150. A method for the reduction of cancer-related pain which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula IIIa



IIIa.

151. The method of Claim 150 wherein the cancer is prostate cancer and the  
5 patient is male.

152. The method of Claim 150 which additionally comprises the  
administration of an anticancer drug.

10 153. The method of Claim 152 wherein the anticancer drug is selected from  
leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D  
analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole,  
cyproterone acetate, and progesterone.

15 154. A method for preventing new bone metastases in a patient which  
comprises administering to the patient in need thereof a therapeutically effective  
amount of an endothelin ET-A receptor antagonist.

20 155. A method for inhibiting metastatic growth in a patient which comprises  
administering to the patient in need thereof a therapeutically effective amount of an  
endothelin ET-A receptor antagonist.

25 156. A method for inhibiting bone turnover in a patient which comprises  
administering to the patient in need thereof a therapeutically effective amount of an  
endothelin ET-A receptor antagonist.

157. A compound according to Claim 1 of formula (I) wherein n is zero; Z is -CH<sub>2</sub>- wherein R<sub>18</sub> and R<sub>19</sub> are hydrogen; R is C(O)-G wherein G is hydrogen; R<sub>1</sub> is aryl substituted with one substituent selected from methoxy, methoxyethoxy, and isopropoxyethoxy; R<sub>2</sub> is 1,3-benzodiox-5-yl; R<sub>3</sub> is R<sub>4</sub>-C(O)-R<sub>5</sub>- wherein R<sub>5</sub> is methylene and R<sub>4</sub> is selected from (R<sub>11</sub>)(R<sub>12</sub>)N- and (R<sub>11a</sub>)(R<sub>12a</sub>)N-N(H)-; one of R<sub>11</sub> and R<sub>12</sub> is hydrogen and the other is selected from arylalkyl and diarylalkyl wherein each aryl group of the diarylalkyl is substituted with methyl or ethyl; and one of R<sub>11a</sub> or R<sub>12a</sub> is alkyl and the other is aryl.

158. A compound according to Claim 1 of formula (I) wherein n is zero; Z is -CH<sub>2</sub>- wherein R<sub>18</sub> and R<sub>19</sub> are hydrogen; R is C(O)-G wherein G is hydrogen; R<sub>1</sub> is phenyl substituted with one substituent selected from methoxy, methoxyethoxy, and isopropoxyethoxy; R<sub>2</sub> is 1,3-benzodiox-5-yl; R<sub>3</sub> is R<sub>4</sub>-C(O)-R<sub>5</sub>- wherein R<sub>5</sub> is methylene and R<sub>4</sub> is selected from (R<sub>11</sub>)(R<sub>12</sub>)N- and (R<sub>11a</sub>)(R<sub>12a</sub>)N-N(H)-; one of R<sub>11</sub> and R<sub>12</sub> is hydrogen and the other is selected from phenylalkyl and diphenylalkyl wherein each phenyl group of the diphenylalkyl is substituted with methyl or ethyl; and one of R<sub>11a</sub> or R<sub>12a</sub> is alkyl and the other is phenyl.

159. A compound according to Claim 1 of formula (II) wherein n is zero; Z is -CH<sub>2</sub>- wherein R<sub>18</sub> and R<sub>19</sub> are hydrogen; R is C(O)-G wherein G is hydrogen; R<sub>1</sub> is aryl substituted with one substituent selected from methoxy, methoxyethoxy, and isopropoxyethoxy; R<sub>2</sub> is 1,3-benzodiox-5-yl; R<sub>3</sub> is R<sub>4</sub>-C(O)-R<sub>5</sub>- wherein R<sub>5</sub> is methylene and R<sub>4</sub> is selected from (R<sub>11</sub>)(R<sub>12</sub>)N- and (R<sub>11a</sub>)(R<sub>12a</sub>)N-N(H)-; one of R<sub>11</sub> and R<sub>12</sub> is hydrogen and the other is selected from arylalkyl and diarylalkyl wherein each aryl group of the diarylalkyl is substituted with methyl or ethyl; and one of R<sub>11a</sub> or R<sub>12a</sub> is alkyl and the other is aryl.

160. A compound according to Claim 1 of formula (II) wherein n is zero; Z is -CH<sub>2</sub>- wherein R<sub>18</sub> and R<sub>19</sub> are hydrogen; R is C(O)-G wherein G is hydrogen; R<sub>1</sub> is phenyl substituted with one substituent selected from methoxy, methoxyethoxy, and isopropoxyethoxy; R<sub>2</sub> is 1,3-benzodiox-5-yl; R<sub>3</sub> is R<sub>4</sub>-C(O)-R<sub>5</sub>- wherein R<sub>5</sub> is methylene and R<sub>4</sub> is selected from (R<sub>11</sub>)(R<sub>12</sub>)N- and (R<sub>11a</sub>)(R<sub>12a</sub>)N-N(H)-; one of R<sub>11</sub> and R<sub>12</sub> is hydrogen and the other is selected from phenylalkyl and diphenylalkyl wherein each phenyl group of the diphenylalkyl is substituted with methyl or ethyl; and one of R<sub>11a</sub> or R<sub>12a</sub> is alkyl and the other is phenyl.